

Examples of Pharmacokinetic Simulations with PK-Sim®: From Physico-Chemical Properties to Concentration Time Profiles

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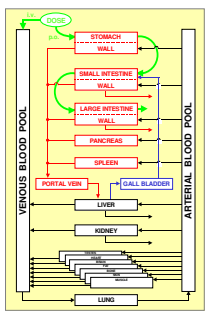
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INTRODUCTION

PK-Sim® is a software for physiology based pharmacokinetic modeling [1]. It combines a universal whole body PBPK-model with a convenient user interface. The possibility to calculate model parameters such as permeabilities and organ/plasma-partition coefficients from physicochemical data with built-in mechanistic models allows the prediction of pharmacokinetics including oral absorption in early phases of drug research. Making use of the full functionality of the software its applicability can easily be extended to the treatment of problems in later phases up to clinical development either in a prospective way or to explain experimental findings.

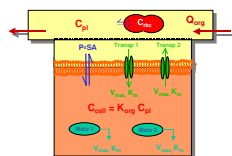
METHODOLOGY

Structure of the PBPK-Model



Key features are:

- Single compartment model of small intestine with plug flow with dispersion of administered dose.
- Description of biliary tract - simulation of EHC possible.
- Permeation barrier for uptake into organs.
- Inclusion of active transporters in each organ.
- Metabolization terms in each organ.



Substance specific parameters of the model are calculated from physicochemical properties (K_{ow} , $P_{SA_{org}}$, $P_{intestine}$) or can be determined in-vitro (K_{ow} , V_{max}).

- Organ/plasma partition coefficients (K_{org}) are calculated from Membrane Affinity [2] and the binding constant for serum albumin, regarding the composition of the organs in terms of lipid, protein and water content [3].
- Permeabilities (P) for tissue uptake are determined according to known dependencies from membrane affinity and molecular weight.
- Passive intestinal permeability ($P_{intestine}$) regards trans- and paracellular transport and an unstirred water layer and is calculated by known dependencies of these contributions from membrane affinity and molecular weight [4].

Pharmacokinetics can be predicted (as long as active processes play only a minor role) with the knowledge of only:

- Lipophilicity (best use with Membrane Affinity = Phospholipid/water partition coefficient)
- Binding to HSA (alternatively unbound plasma fraction)
- Molecular weight
- Intestinal solubility
- In-vitro metabolization rates

EXAMPLE 1

Ciprofloxacin: Organ concentrations in Rats

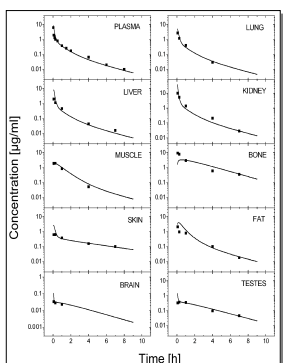
Experimental data used:

log(Membrane affinity): 1
log(K_H (HSA)): -2.7
 M_w : 331
 Cl_{int} [ml/min/kg]: 5
 Cl_{ext} [ml/min/kg]: 20

Parameters of Experiment:
Species: Rat
Dosing: 5 mg/kg, i.v. bolus

Results:

Starting from physicochemical properties and in-vivo clearance values an excellent simultaneous description of the kinetics in the various organs can be achieved.



EXAMPLE 2

Theophylline: Plasma and Muscle concentrations in Humans

Experimental data used:

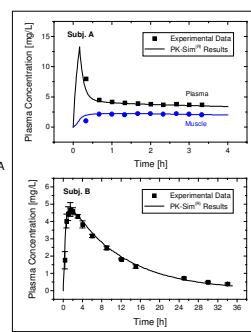
logP: -0.20
log(K_H (HSA)): -2.89
 M_w [g/mol]: 180
 Cl_{int} [ml/min/kg]: 0.25 (Subj. A)
 Cl_{ext} [ml/min/kg]: 0.50 (Subj. B)

Parameters of Experiment:

• Species: Human
• Dosing: 240 mg i.v. (10 min.) Subj. A
• Dosing: 200 mg p.o. Subj. B

Results:

Intravenous as well as oral application of a small, hydrophilic compound can be modeled.



Experimental data taken from:
Müller et al., *Naturwissenschaften* 352 (1995)
Meyer et al., *Biofarm. Drug Dispos.* 20 (1983)

EXAMPLE 3

Haloperidol: Individual variations, controlled release

Experimental data used:

log(Membrane affinity): 3.72
 f_u (Plasma): 4.6% (Subj. A)
 f_u (Plasma): 2.0% (Subj. B)
 M_w [g/mol]: 376
 Cl_{int} [l/h/kg]: 0.11 (Subj. A)
 Cl_{int} [l/h/kg]: 0.15 (Subj. B)

Parameters of Experiment:

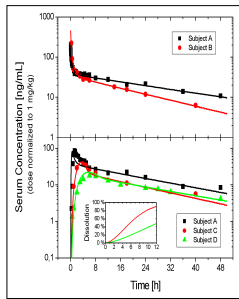
Species: Human
Dosing: 1 mg/kg, i.v. bolus
1 mg/kg p.o.

Results:

Intravenous as well as oral application of a highly lipophilic compound can be modeled.

⇒ Inter-subject variability can be explained by individual variations in protein binding and clearance

⇒ Different formulations can be modeled using an appropriate dissolution profile



Experimental data taken from:
Mitra et al., *J. Pharm. Sci.* 78 (1989)
Holley et al., *Clin. Pharmacol. Ther.* 33 (1983)
Forsmann et al., *Curr. Therap. Res.* 20 (1976)

EXAMPLE 4

Digoxin: Influence of intestinal P-gp transporters

Experimental data used:

log(Membrane affinity): 1.48
log(K_H (HSA)): -3.7
 M_w [g/mol]: 390
 Cl_{int} [ml/min/kg]: 1.90
 K_m (P-gp) [μ M]: 16
 V_{max} (P-gp): Relation between values in different sections of the small intestine according to expression profile of P-gp [5] (absolute value fitted).

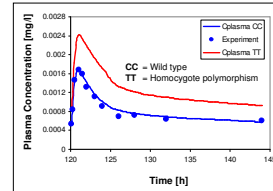
Parameters of Experiment:

• Species: Human
• Dosing: 0.25 mg p.o.
• Application: Once daily for 6 days.
• Plasma concentrations determined at day six.

Results:

Influence of active transport on bioavailability can be described very well.

⇒ Facilitates predictive Pharmacogenomics!



Experimental data from:
A. Johnie et al., *Clin. Pharmacol. Therap.*, 66 (1999)

Polymorphism	Expression level (%)	C_{max} in Plasma in vivo (ng/l)	C_{max} in Plasma in silico (ng/l)
CC	100	1.7	1.7
TT	46	2.2	2.4

Experimental data from:
S. Hoffmeyer et al., *PNAS*, 97 (2000)

SUMMARY AND CONCLUSIONS

PK-Sim® is well suited to simulate the pharmacokinetics of compounds having very different physical and chemical properties. The shown examples cover a broad range from a small hydrophilic drug molecule (Theophylline) to a highly lipophilic compound (Haloperidol).

Only basic physicochemical input parameters such as lipophilicity, plasma protein binding, and molecular weight plus information about the metabolization rates are required for compounds with passively driven absorption and distribution kinetics. More complex pharmacokinetic scenarios such as active transport can also be modeled, if the information about such processes is available from in-vitro experiments.

Simulations for a compound validated by good correlation to already obtained experimental PK data can be used as starting point for prospective simulations of the same compound in different situations. Examples are species extrapolations or sub-populations, or the description of controlled release oral formulations.

REFERENCES

- [1] <http://www.pk-sim.com>
- [2] A. Loidl-Stahlhofen, T. Hartmann, M. Schottner, C. Rohring, H. Brodowsky, J. Schmitt, J. Keldenich, *Pharm. Res.* 18, 1782-1788 (2001)
- [3] M. Härter, J. Keldenich, W. Schmitt in: *Combinatorial Chemistry - A Practical Handbook, Part IV*, Eds. K. C. Nicolau et al., Wiley VCH, Weinheim, 2002
- [4] Leahy et al. in: *Novel Drug Delivery and Its Therapeutic Application*, L. F. Prescott, W. S. Nimmo, Eds. (1989)
- [5] Brady et al., *Drug Metab. Dispos.* 30, 838 (2002)



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