

PBPK-modeling as a tool for interpreting and understanding pharmacokinetics

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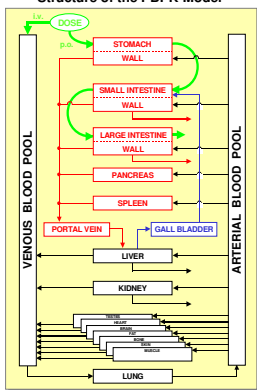
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INTRODUCTION

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 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. The examples shown here demonstrate for some cases how the combination of simulation and experiment opens new opportunities for a faster and broader assessment of pharmacokinetics.

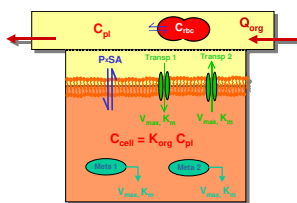
METHODOLOGY

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.

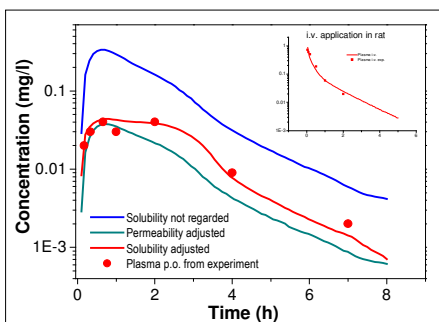


Substance specific parameters of the model are calculated from physicochemical properties (K_{org} , $P_{XSA_{org}}$, $P_{intestine}$) or can be determined in-vitro (K_{int} , V_{max}).

- 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].

Poor Bioavailability: Is it solubility or permeability?

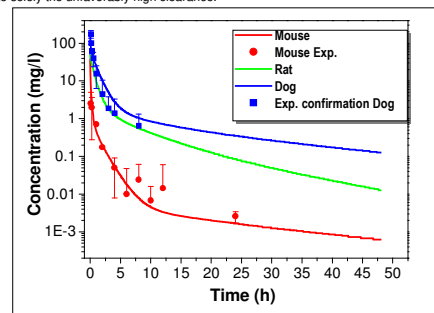
For a compound with unknown solubility the i.v. plasma curve in rats could be well described but the simulation of p.o. application led to a much to high bioavailability.



- Low permeability and solubility were tested as alternative hypotheses.
- Better fit of curve form with low solubility led to identification of solubility as limiting factor. This finding was experimentally confirmed afterwards.

Species dependent distribution kinetics

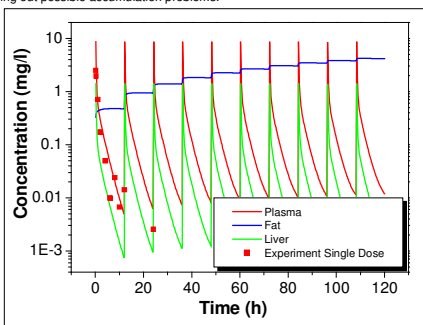
A compound with high (blood flow-limited) clearance showed rapidly decreasing plasma concentrations in mice after i.v. application. This problem was first attributed to solely the unfavorably high clearance.



- Simulations demonstrated that larger species should exhibit much higher plasma concentrations due to different distribution kinetics (even in case of blood flow-limited clearance).
- The higher plasma concentrations were afterwards confirmed for dogs.

Unexpected accumulation behavior

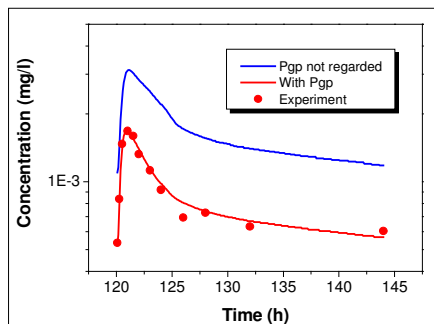
A rapid decrease of the plasma concentration suggest a similar behavior in all organs ruling out possible accumulation problems.



Simulations over longer periods with multiple administrations show that depending on physicochemical substance properties and physiological differences (blood flow rates, volumes) the behavior in the different organs can be very different and also strongly deviating from the plasma curve.

Influence of intestinal P-gp transporters (Example: Digoxin)

Simulation of Digoxin on the basis of physicochemical data and in-vivo clearance information leads to a higher bioavailability and broader peak compared to experiment.



Introduction of excretional active transport with adjusted V_{max} values but regarding the relative distribution of P-gp in different gut sections leads to a perfect description of the plasma curve obtained in vivo.

SUMMARY AND CONCLUSIONS

- PBPK-simulations with PK-Sim[®] on basis of physicochemical data and clearance information obtained in vitro or in vivo yield good predictions of pharmacokinetics as long as distribution is determined by passive processes.
- Discrepancies between simulation and experiment are hints for effects which are not regarded in the simulation model used and enable the disclosure of information hidden in the experimental results by hypothesis testing.
- PBPK-simulations can add a vast amount of information to experimental pharmacokinetic data and can thereby significantly support the judgement of a compound.

- PK-Sim[®] is a valuable tool, opening new opportunities for the interpretation of experimental results.
- The combination of experiment and PBPK-simulation can speed up drug development significantly.

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)
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- [4] Leahy et al. in: *Novel Drug Delivery and Its Therapeutic Application*, L. F. Prescott, W. S. Nimmo, Eds. (1989)



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