PBPK-modeling as a tool for interpreting and understanding pharmacokinetics

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INTRODUCTION
PB-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 permeability 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 permeation barrier for uptake into organs.
• Permeation barrier for uptake into organs.
• Metabolization terms in each organ.

Key points are:
• Substance specific parameters of the model are calculated from physicochemical properties (K₄ determined in-vitro (K₄ absorption in early phases of drug research. Making use of the full development either in a prospective way or to explain experimental findings. 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. The combination of experiment and PBPK-simulation can speed up drug development significantly.

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.

REFERENCES

Bayer Technology Services