The minipig in PBPK modeling

PK-Sim® from Bayer Technology Services is a commercially available tool for physiologically-based pharmacokinetic (PBPK) modeling of drugs in laboratory animals and humans. The aim of PBPK modeling is to describe mathematically all physical and physiological processes that determine the uptake, distribution, and elimination of a compound in an organism in as much detail as possible. PBPK modeling can be used as a tool for an early in silico prediction of ADME properties of new compounds.

In short, PK-Sim® is a generic PBPK model with 17 organs and tissues. Represented organs/tissues include arterial and venous blood, adipose tissue (separable adipose, excluding yellow marrow), brain, bone (including yellow marrow), gonads, heart, kidneys, large intestine, liver, muscle, portal vein, pancreas, skin, small intestine, spleen and stomach. Each organ further consists of four sub-compartments namely the plasma, red blood cells (which together build the vascular space), interstitial space, and cellular space. PK-Sim® estimates model parameters (organ partition coefficients, permeabilities) from physico-chemical properties of compounds and from the composition of tissues in terms of lipids, water and protein. The physico-chemical properties needed as input information are lipophilicity, plasma protein binding constant or alternatively the fraction unbound in plasma, and molecular weight. In addition to physico-chemical inputs, compound specific clearance information (either in vivo plasma or blood clearances or intrinsic clearances determined from in vitro experiments) are required. As output information, PBPK modeling allows to predict the pharmacokinetic behavior of a compound on the basis of these parameters. Moreover it is a powerful tool for investigating the sensitivity of pharmacokinetics with respect to them.

In light of the increasing interest in the minipig as a favorable model for pharmacokinetic studies, a minipig module has been developed and implemented in PK-Sim®. Thus, besides the established human module and the animal models of the monkey, dog, rat, and mouse, PK-Sim® now allows the simulation of pharmacokinetics in the minipig. To evaluate how suitable the new module is for the prediction of pharmacokinetics in the minipig, a PBPK model of the nonsteroidal anti-inflammatory drug diclofenac administered intravenously and orally was first set-up for humans and then extrapolated to the minipig.

Detailed information on methods and the results of the diclofenac study is given in the below-mentioned poster presented at the 2nd Pharmaceutical Sciences Fair and Exhibition in Nice, France (June 8-12th 2009).

For further information on the PBPK software, PK-Sim®, please visit the webpage www.systems-biology.com/products/pk-sim.html or contact info@systems-biology.com.

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Introduction

- Due to similarities between man and pig with regard to physiology and biotransformation, pigs are valuable non-rodent research models
- Among pigs, miniature breeds were developed for the special demands of preclinical experiments
- The minipig can be used successfully for intravenous (i.v.), oral, and dermal studies

Purpose

- Development of a minipig module and implementation into the commercial physiologically-based pharmacokinetic (PBPK) software tool PK-Sim®

Methods

1. Implementation of physiological information[1,2,3] into the model database of PK-Sim®[4]

2. Evaluation of the new module: Extrapolation of diclofenac pharmacokinetics (PK) from human to the minipig

2.a) Development of the PBPK model in humans following i.v. administration of diclofenac

2.b) Prediction of diclofenac PK in humans following oral administration

2.c) Prediction of diclofenac PK in the minipig following i.v. and oral administration

Table 1: Physico-chemical parameters of diclofenac

Parameter	Value
logMA	2.94
fu	0.2%
MW	296 g/mol
pKa (acid)	4.15
Solubility	5.61 mg/L

Input parameters and model parameterization

- Physico-chemical data of diclofenac was taken from the literature[5,6] (Table 1)
- Species-specific data and application parameters were adjusted to values reported in each of the two studies used for comparison[7,8]
- Distribution model: 4 subcompartments per organ[9]
- Adjustment of the endothelial permeability between plasma and interstitium: 0.1 cm/s for all organs with the exception of the liver (10 cm/s) → the high protein binding of diclofenac (>99.5%) is expected to restrict the passage of the compound from the plasma into the interstitium. The liver sinusoidal wall, however, contains open pores (fenestrae) which facilitate permeability into this organ[10]
- Diclofenac plasma clearance was implemented according to the reported values (253 mL/h/kg in humans and 52 mL/h/kg in the minipig)[7,8]
- For the oral study in humans, a lag time of 30 min and the in vitro dissolution profile of Voltaren® enteric-coated (EC) tablets at pH7 was included in the model to account for the delay in diclofenac release from the orally administered EC tablets[11]
- Simulation of two different cases: 1. in consideration of charge-dependent distribution and solubility (——) and 2. without taking charge-dependent distribution and solubility into account (·······)
- The two cases show almost identical distribution behavior (Fig.1) whereas there is a considerable difference in their predicted absorption kinetics (Fig.2)

Figure 1: Simulated and observed plasma concentration-time profiles following i.v. administration of 50 mg diclofenac Na to humans
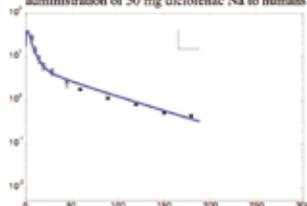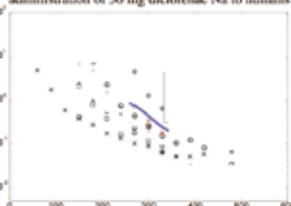
Figure 2: Predicted and observed plasma concentration-time profiles following oral administration of 50 mg diclofenac Na to humans

Results and Discussion

- Using the identical model previously established in humans the plasma concentration-time profiles following i.v. administration of 25 and 50 mg diclofenac sodium to minipigs could be very well predicted (Fig.3)
- Following oral administration of different solution types (50 mg diclofenac sodium in a solution of 50 mL phosphate buffer pH 7.4, 50 mL water or 200 mL water), the differences in diclofenac absorption were perfectly predicted by the software (Fig.4)
- Obviously, in case of the 50 mL unbuffered solution, the drug precipitates in the GI tract, as predicted by the software considering pH-dependent solubility. By contrast, both buffering and increased intake volume could increase the absorption rate of diclofenac, which could be better predicted assuming pH-independent solubility

Figure 3: Predicted and observed plasma concentration-time profiles following i.v. administration of diclofenac Na to minipigs
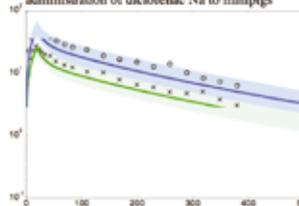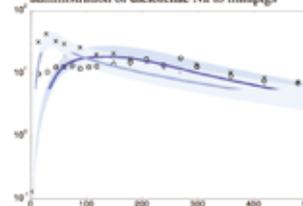
Figure 4: Predicted and observed plasma concentration-time profiles following oral administration of diclofenac Na to minipigs

- The effect of different dissolution profiles to reflect potential precipitation of diclofenac was investigated within the scope of a sensitivity analysis
- The three administration scenarios could be well simulated (Fig.6) assuming the highlighted dissolution profiles (Fig.5)

Figure 5: Empirical dissolution profiles used to investigate the dissolution behavior of precipitated diclofenac from different solution types
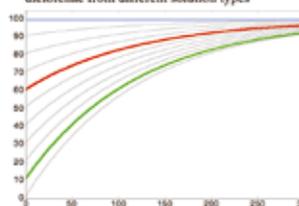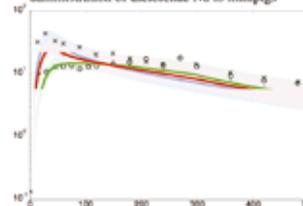
Figure 6: Simulated and observed plasma concentration-time profiles following oral administration of diclofenac Na to minipigs

Conclusions

- The established human diclofenac model could be easily extrapolated to the minipig
- Differences in diclofenac absorption due to pH-dependent solubility in the GI tract were simulated well with the PBPK model
- The possibility of predicting PK in the minipig and/or extrapolating data from one species to another is a valuable tool for (pre-)clinical development, facilitating dose adjustments for species, enabling efficient blood sampling protocols and potentially resulting in a reduction of the number of animals/subjects required for the study

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