Integration of preclinical information into a PBPK approach for predicting human pharmacokinetics

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INTRODUCTION

▪Physiology-based pharmacokinetic (PBPK) models are currently under scrutiny for predicting the pharmacokinetics in preclinical models and in humans [1-8].

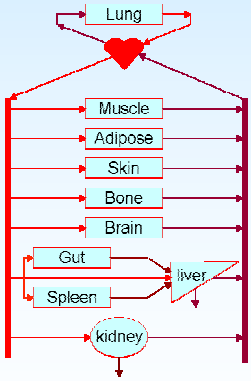

Fig.1. Scheme of the basic whole body PBPK model.

▪The basis of the implementation of PBPK in this area is the predictions of the clearance contributions (using intrinsic clearance from liver preparations) and of the tissue partition coefficients. Some *in silico* approaches have been proposed for predicting the tissue partition coefficients, based on lipophilicity (logP), acid-base characteristics, and fraction of drug unbound in plasma [8-13].

▪This approach has some rigidity as it is influenced by assumptions on drug-specific parameters, which may be violated in some cases. For instance, the fraction of drug unbound in tissues is calculated as a function of the fraction unbound in plasma only [1] and there are uncertainties regarding the influence of the binding to plasma and liver preparations for the scaling of the total clearance.

▪In addition, in the currently proposed approaches, *in vivo* pharmacokinetic in preclinical species are only used to confirm that the *in silico* methodologies are able to predict the PK characteristics in animals [6], whilst these data are not used for actually performing the human predictions.

OBJECTIVES

We are proposing and evaluating a PBPK approach in which all the non-clinical information are considered. A Bayesian approach was applied to *in vivo* preclinical data to identify a few critical parameters known with some uncertainty, thereby relaxing some assumptions and possibly improving the predictive performance of the basic PBPK. We evaluated the performance of such approach to predict human pharmacokinetics.

METHODS

▪A basic, generic whole body PBPK model was implemented for rats, dogs and humans (Fig.1).

▪Hepatic clearance CL_H and tissue partition coefficient $P_{T:P}$ were computed as follows:

$$CL_H = \frac{(CL_{int,H}(f_{uP}/f_{uH})) \times Q_H}{(CL_{int,H}(f_{uP}/f_{uH})) + Q_H}$$

where $CL_{int,H}$ = intrinsic clearance from liver preparations, f_{uP} = fraction of drug unbound in plasma, f_{uH} = fraction of drug unbound in liver preparations, Q_H=blood flow perfusing the liver;

$$P_{T:P\,non\text{-}adipose} = \frac{P_{O:W}(V_{nlT} + 0.3V_{phT}) + (V_{wT} + 0.7V_{phT})}{P_{O:W}(V_{nlP} + 0.3V_{phP}) + (V_{wP} + 0.7V_{phP})} \times \left(\frac{f_{uP}}{f_{uT}}\right)$$

where $P_{O:W}$=n-octanol:water partition coefficient, V_{wT}, V_{nlT}, V_{phT} are fractional weight of water, neutral lipids and phospholipids in tissue T, respectively, V_{wP}, V_{nlP}, V_{phP} are the corresponding values in plasma, f_{uT} = fraction of drug unbound in the tissue, and where:

$$f_{uT} = \frac{1}{1 + (((1 - f_{uP})/f_{uP}) \times c)}$$

▪The predictive performance of the basic model in these species was initially evaluated using a dataset of 23, 21 and 8 compounds for rats, dogs and humans, respectively.

▪A Bayesian approach, as implemented in SAAM II™ 1.1.2 (SAAM Institute, University of Washington, Seattle) was used to identify a few critical parameters, known with some uncertainty, to provide a better adherence of the predictions in rats and dogs with the corresponding observations.

▪The parameters considered critical (after a sensitivity analysis on the PBPK model) and to be identified using the Bayesian approach were: f_{uP}, $P_{O:W}$, c and $f_{uP}/f_{u,H}$

▪The parameters identified in rats and dogs were used to simulate the pharmacokinetics in human subjects.

RESULTS

▪The basic model applied to the preclinical species showed average fold-errors for the main pharmacokinetic parameters of less than 2, with 91% of the compounds predicted within a 3-fold error.

▪The new approach is summarized in Fig. 2.

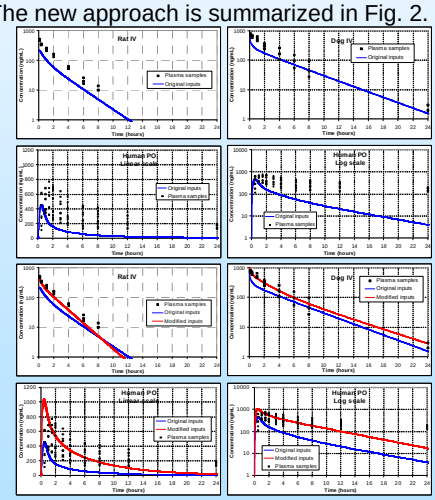

Fig.2. Scheme of the application of the new approach

RESULTS (cont'd)

Table 1. Modulated parameters and performance evaluation for the basic and new approach applied to the compound described in Fig. 2.

	critical inputs				fold error	
	fuP	logP	c	fuP/fuH	Cmax	AUC
Basic approach	0.004	4.1	0.50	1.00	1.2	7.5
New approach	0.005	3.9	0.24	0.43	2.0	2.1

Six of the eight compounds given to humans were reasonably well predicted in the preclinical species. For these compounds the statistics obtained for human predictions improved significantly applying the new approach, compared to the basic one.

Table 2. Performance statistics for the basic and new approach applied to the PK prediction of oral dosing in humans for six compounds

	average fold error	
	Cmax	AUC
Basic approach	**4.1**	**3.5**
New approach	**3.4**	**2.0**

For the other two compounds, the PBPK predictions obtained in humans with the original inputs were strongly biased. Applying the new approach the bias was reduced (from 55 to 8-fold and from 385 to 39-fold for the prediction of AUC), even if it remained unacceptably high. Causes of this high bias were the dynamic range of the intrinsic clearance estimation for one compound and the involvement of transporters in the disposition of the other compound.

CONCLUSIONS

▪The predictions from a basic PBPK model were improved applying a Bayesian approach by fine tuning a few model parameters based on *in vivo* animal data. The results obtained so far are promising; however, they need to be confirmed on a more extensive dataset of compounds.

▪It may be too optimistic to provide a generally applicable 'receipt' to the prediction of the pharmacokinetics in humans. The approach need to consider the specificities of each compound. The knowledge obtained from the evaluation of compounds of the same class should also be considered.

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