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Human Pharmacokinetics Prediction

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Editorial

Drug development is very time consuming and costly process. Only few candidates enters in to clinical trials can eventually become a drug. Accurate prediction of the right dose before entering in to clinical study can reduce time as well as cost of drug discovery process. Pharmacokinetic plays an essential role in the selecting the right dose and dosage regimen [1-5]. Thus early prediction of human pharmacokinetic based on animal and *in-vitro* data is the challenging task for the scientist. Predictions of human pharmacokinetic parameters include the clearance, volume of distribution, half-life, bioavailability, effective dose and dosage regimen, plasma concentration time profile; inter individual variability and drug-drug interaction. There are numerous methodologies available in the literature for human prediction. Most widely used methods are the *In-vitro In-vivo* Extrapolation (IVIVE), allometric scaling and Physiologically Based Pharmacokinetic modeling (PBPK) [6-8]. Best results in the prediction can be obtained by applying one or two methods in a combination.

In-vitro in-vivo extrapolation

IVIVE approach utilizes the *in-vitro* metabolic clearance and protein binding data to scale to *in-vivo* clearance. Major route of the elimination for most of the drugs are through biotransformation such as Phase I (CYP mediated) and Phase II (Conjugated enzyme through). In this methodology *in-vitro* studies with hepatocytes or liver microsomes can be used for the scaling. There are basically three models available to calculate *in-vivo* clearance such as well-stirred, parallel tube and dispersion models. Among all three models well stirred model is widely used model because of its mathematical simplicity. These liver models predict the *in-vivo* clearance based on some assumptions such as: 1) Only unbound drug can cross the membrane and interact with the enzymes; 2) There is no diffusion barrier exist and drug distribution is perfusion rate limited; 3) Metabolic enzymes are homogenously distributes in the liver. Basically two steps involved in this methodology. First step is to scale intrinsic clearance to *in-vitro* hepatic clearance by using the appropriate scaling factors. In second step it further reconstructed by applying the blood flaw and binding (Protein and microsomal binding) parameters [9-11].

Allometric scaling approach

Allometric scaling is widely used for the human clearance prediction based on animal data. Allometric is the study of size and its consequences. Its empirical form based on mathematical equation to extrapolate pharmacokinetic parameters to the species of the interest. Many important PK parameters such as clearance, volume of distribution and half-life are predicted using this methodology. Al though this approach is very widely used but major drawback is not to consider the metabolic differences among the species. Allometry can be used for the interpolation and extrapolation but variability is very high in the extrapolation perticulaterly when predicting from small animal to humans. There are many methods available in this approach to predict human pharmacokinetic parameters such as: Simple allometry; Single species allomteric approach; Rule of exponents; Allometric scaling of unbound clearance; Allometric scaling for renally and biliarily excreted drugs and fu (Fraction unbound) corrected intercept method. Over the years many improvements have been included in the allometric scaling approach for better prediction [12-15].

Physiologically Based Pharmacokinetic Approach (PBPK)

PBPK was first described by Teorell in 1937. PBPK modeling gains much attention in recent past due to its more holistic and dynamic approach for the modelling. In this approach drug dependent parameters (Solubility, Log D, pKa, Metabolism, Protein binding, Blood partitioning etc.) and system dependent parameters such as (Tissue volume, Tissue composition, Blood flaw etc.) utilized to generate the structural model using mathematical equations. This structural model utilized to predict the plasma and tissue pharmacokinetics. PBPK is more often used in the drug discovery to predict early pharmacokinetics in the humans to minimize the late failures. Moreover it utilizes to predict the drug-drug interaction as well as dosage regimen in the children. PBPK has advantage over the IVIVE and allomteric scaling because it utilize all the factors which leads to predict the pharmacokinetics [16-19].

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