LITERATURE REVIEW ON ESTIMATION OF DRUG PARAMETERS USING PHYSIOLOGICALLY-BASED PHARMACOKINETIC MODELING

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Abstract

Physiologically based pharmacokinetic (PBPK) modelling is a computing technique used to identify the pharmacokinetic properties of humans and other animal species. This technique is used to identify various drug parameters. One of the parameters is bioavailability. Bioavailability is defined as the fraction of substances being absorbed by the body. Contrasts in bioavailability, realizing whether drug formulations are identical is necessary. The area under the plasma concentration time curve which is AUC determines the bioavailability of the drug. PBPK model is a significant modelling to determine the pharmacokinetic parameters. The goal of this paper is to review various literature which uses PBPK model in different pharmaceutical applications in different populations evaluating, verifying, predicting and identifying different pharmacokinetic and drug parameters.

Keywords: Bioavailability, PBPK model, Pharmaceutical, Drug

INTRODUCTION

PBPK models describe the organism as a set of tissue compartments interconnected by blood (plasma) flow. It consists of systems of differential equations based upon mass balance. PBPK model captures biological processes and hypotheses expressly describes variable degrees of detail or biological realism and adaptability to mirror biology. It will incorporate changes in PK because of chemical, growth/aging and facilitates analyses across species, doses and human population subgroups. The percentage of drug absorbed is the bioavailability of the drug. Bioavailability is one of the most important pharmacokinetic properties of a drug [2].

In this paper, literatures related to physiologically based pharmacokinetic model has been reviewed. The simulation of PBPK model for various pharmacokinetic applications in different software platforms have been discussed. The papers between 2004 and 2020 have been reviewed.
1. Literature Review

Mathematical models have been utilised to comprehend different aspects of diabetes mellitus (DM). The author has developed mathematical models to check blood sugar dynamics in DM in two significant groups, that was classified in line with the quality of their description. One such group was the whole-body model created under PKPD approach with limited physiological interpretation. Other groups used physiologically based PKPD models to depict the physiological relationship between different subsystems of the human body mathematically. The PB-PKPD models, which are an organ-based compartmental model that simulates blood glucose dynamics, were used in this study [3]. Then the resulting function was fitted to clinical data of healthy people.

Clinical evidence for this study came from peer-reviewed publications. The author used state space theory to find the system’s solution as the vector that defined the time evolution. After intravenous glucose infusion and oral glucose ingestion, the mathematical model simulated the blood glucose dynamics of a healthy human body [3]. The parameters of a mathematical model for type 2 diabetes mellitus were fitted using a static and dynamic fitting approach. The T2DM model was developed by the researcher. The established method was effective in simulating the dynamics of blood glucose. Moreover, the author concluded that their model can be utilized to build up a feedback model-based controller for blood glucose regulation in T2DM patients PKPD model was considered as a good approach to develop a model for T2DM which includes the physiological parameters that help in finding improved glucose metabolism.

1.1 Pharmacokinetics and population pharmacokinetics in paediatric oncology

The study and treatment of childhood cancer is known as paediatric oncology. The majority of cancers seen in children vary from those seen in adults. Cancers in infants, children, and teenagers are the subject of paediatric oncology. Whether the treatment includes chemotherapy involves a combination of chemotherapeutic agents. For this it is important to identify the exposure of drug which should be within the therapeutic window. Pharmacokinetics and pharmacodynamics studies help in identifying the relationship between dose and concentration and also the effects of drugs within the human body. Unfortunately, due to the limited population of paediatric oncology, there is a lack of PK/PD results. As a result, the author used the population PK (POPK)/PD modelling approach, which has a number of benefits, including the ability to sample at any time and with a small sample size [4]. In this paper, the author provided the fundamental interpretation of PK and POPPK through examples.

Ten examples were discussed which utilizes the POPPK approach and have described the basis of POPPK approaches. Author concluded that, although the POPPK approach has some advantages, the clinical implications are not always obvious and translation to the clinic can be difficult. PK studies have helped paediatric oncology with individualised and optimised dosing. Because of the time flexibility of blood sampling, the use of heterogeneous data, quantification and identification of variability, and simulation, the POPPK model was found to be an ideal method for considering PK in children.
1.2 Development and application of PBPK in of internal dose of pyrethroids is human

The literature focuses on demonstration of a life stage PBPK modelling approach is conjoined with invitro to in vivo extrapolation (IVIVE), that helped in evaluating the pharmacokinetics of age dependent changes of internal target tissues exposure in humans of 8 pyrethroids. The structure of PBPK model implies it was a multi-compartmental model taken account of a large dataset of anatomical and physiological parameters of different stages of age. This model was combined with the IVIVE model, which allowed for the integration of human related metabolism data and age-dependent changes, resulting in improved age-specific target tissue exposure prediction capability [1].

The parameters involved in this model includes physiological parameters (body weight (BW), cardiac output, tissue weights, tissue plasma flows), chemical - specific parameter which was taken from the rat model based on similarities between rat and human and enzyme ontogeny was used to predict the age-specific metabolic clearance of pyrethroids in vivo. The author developed the model in acsIX. With monte-carlo analysis of four different ages, the model was run for eight pyrethroids with a daily oral dose of 1 mg/kg. The creation and implementation of an IVIVE-supported life-stage human PBPK model [5] for the evaluation and prediction of age-related pyrethroid sensitivity was described in this literature [5]. The research demonstrated that life stage IVIVE - PBPK modelling supports risk assessment for sensitivity of pyrethroids to different age groups.

1.3 Physiologically based pharmacokinetics modelling in MATLAB

In this paper the framework for physiologically based pharmacokinetic modelling and steps involved to build a PBPK model using MATLAB have been described. A mathematical modelling technique for predicting the absorption, distribution, metabolism, and excretion (ADME) of synthetic or natural chemical substances in humans and other animal species is physiologically dependent pharmacokinetic modelling [6]. Several platforms were used for building a PBPK model such as SimCyp, Pk-sim and Gastroplus.

In this paper [6] they have explained the steps to build a PBPK model in MATLAB. There are five steps involved in building a PBPK model. This was illustrated in the paper. The first step involved in defining the parameters of the model which includes physiological parameters and drug parameters. Then the population was generated based on the age parameters. After that calculations were made for required drug parameters. After the steps, system and drug data bridge using ODE solver. The model was created using the steps after that we can work with the simulated data. The major advantages of PBPK model includes it was a population specific model such as pregnant women children elderly organ impairment and we can evaluate PD after PBPK simulation. In this literature, PBPK model simulation was explained with an example of simulation of clinical scenarios of aging HIV infected patients of drug darunavir, Ritonavir and Rivaroxaban [6]. Hence the paper described a comprehensive strategy to develop a PBPK model in MATLAB.

Darunavir is a second-generation antiviral that has been approved to treat HIV-1 infection. The aim of this research was to create and validate a darunavir population pharmacokinetic model based on data from daily practices. Data sets were obtained from a pair of hospitals. From this data pharmacokinetic model was developed. The model was developed using the iterative two stage Bayesian procedure. The software package MWpharm was used to develop the model. The passing - Bablok analysis revealed that the measured and expected
concentrations were linearly related. A solid population pharmacokinetic model was built in this literature, which could help with therapeutic drug observance of darunavir in regular patient settings [7].

In the literature [8], the author established the PBPK based predictions using paediatric ontogeny [8] information. The model was developed using a consistent PBPK translation of adult pharmacokinetics of a small molecule to children, as well as knowledge of the ADME (absorption, distribution, metabolism, and elimination) [8] process in adults and ontogeny data. In this article, the author translates the model from adults to children. PBPK modelling would then be able to be utilized to tentatively set up the relationship between dose and exposure in children of different ages. Ontogeny data could be obtained from a variety of sources, including (semi) quantitative mRNA expression or in vitro activity data, as well as deconvolution of in vivo pharmacokinetics data. The methods used to simulate the model were PK-Sim and MOBi. Bridging a PBPK model for adults to children is part of the workflow. There are several articles confirming effective PBPK prediction in children including established ontogeny functions with data observed during clinical studies in children [8]. The OSP software suite consists of PK - sim and MOBi provides functionality. The software tools for PBPK model integrated the translation workflow. Author concluded that the approach provided them full traceability and transparency for regulatory agencies.

Aging is the characterization of anatomical, physiological and biological changes that affect drug kinetics. There is only sparse knowledge on elderly pharmacokinetics as they were often excluded from the clinical trials. PBPK model overcame this limitation. It is enough to inform models with detailed descriptions of the population. The research is focussed on development and verification of the population database for aging Caucasians considering anatomical, physiological and biological system parameters which were required to inform the PBPK model that included population variability [9]. Parameters were obtained. Then, mathematical models from the literature equations were derived from all the collected data. It is observed that, developed population was implemented in MATLAB where the estimated system parameters were in accordance with independent observed data showing robustness of the developed population [9]. Repository of parameters needed for the PBPK model was developed which will be helpful for analysing drug kinetics and drug-drug interaction in the elderly.

1.4 Physiologically based pharmacokinetics modelling for first in human predictions

This literature [10] consists of review of many relevant publications identifying new findings and limitations of first - in - human physiologically based pharmacokinetic model building strategy. It was identified that the quality of first -in- human PBPK predictions was greatly improved when inputs available for most critical parameters [10]. From the review of several publications in this literature it was observed that uncertainty analysis was the key consideration to get maximal value from the first-in-human PBPK model. It was observed that verification of the first - in - human PBPK model was very important in assessment of clinical trials. It is evidence that physiologically based pharmacokinetics modelling allows assessment of the complications of the limitations in model inputs [10].
1.5 Predictive performance of PBPK modeling of drugs extensively metabolized by cytochrome P450 in children

This literature aimed at the characterization of the paediatric predictive performance of the PBPK approach for the 10 drugs metabolized by CYP1A2 (theophylline), cyp2c8 (desloratidine, montelukast), cyp2c9 (diclofenac), cyp2c19 (esomeprazole, lansoprazole), CYP2D6 (tramadol), and CYP3A4 (itraconazole, ondansetron, sufentanil) [11]. Model performance was evaluated using comparison of plasma concentration time profiles of predicted values with the observed clinical results of children for each drug and age group. In this literature, the PBPK model for children was simulated using the software simcyp. It was concluded that the developed PBPK model can reasonably predict exposure in children [11] aged 1 month and older for CYP metabolized drugs array.

Physiologically based pharmacokinetic modelling is viewed as a significant tool for anticipating pharmacokinetic changes in pregnancy to guide [12] in vivo pharmacokinetic trials in pregnant women. The literature aims in extending and verifying the previously developed physiologically based pharmacokinetic model for pregnant women for the prediction of pharmacokinetics of drugs metabolized via several cytochrome P450 enzymes [12]. Data available from the literature was taken as input parameter and it was evaluated using the pharmacokinetic model and predicted the pharmacokinetics of eight drugs. The predictions of the PBPK model were evaluated by comparing with the data obtained from the literature. While evaluating the model ninety-seven percent of mean plasma concentration predicted in pregnant women fell within a twofold error range. It was concluded that pregnant physiologically based pharmacokinetic models identified the potential exposure changes and support decision making during clinical trials in special populations.

The article [13] aims to give a comprehensive account of paediatric clinical literature between 2006 and 2016. Case examples were reviewed in this article. It was identified that overall performance of paediatric PBPK modelling approaches adequately predict observed data [13]. It was considered that performance of the paediatric modelling approach was analysed and found that 80% of PBPK models predicted within 1.5-fold of observed parameters for all populations. The paper reviewed both direct and indirect methods of paediatric PBPK model for determining dose determination. It was found that average accuracy was about 80% across paediatric age groups. PBPK models are expected to become indispensable in the evaluation of drugs in paediatric populations [13].

In the paper [14] they have discussed the early oral bioavailability prediction using following approaches. 1) Quantitative structure property relationship [14] (QSR) 2) Rule of thumb (ROT) and 3) Physiologically based pharmacokinetic modelling QSPR model uses classification regression approach under SVM, MCR, and ANN. It was observed that QSPR and ROT models have some limitations where it was a more complex and dynamic phenomenon. PBPK models integrate both physiological processes with physicochemical properties. Insilico, invitro and in vivo parameters were given as input which combined to predict plasma and tissue concentration time profile [14]. Tools used in the literature include symbiology, MATLAB, Gastroplus, PICSIM. PBPK models are very useful during the early drug delivery process.
Vancomycin PBPK model [15] was developed. The author developed model which predicted the concentration time profiles in healthy adults and diseased patients. The Implementation [15] was done in both renal and non-renal elimination pathways to paediatric model that predicted the vancomycin clearance [15]. The Software used to build the model was Simcyp simulation software. It was observed that Volume and distribution of the drug vancomycin was 0.37L/kg. The Residual clearance was about 0.8 micro ltr/min/million cells.

In the paper [16], several case studies were discussed on how PBPK [16] modelling and simulation can be utilized through various stages of drug discovery and development. The Tools used for the simulation were GastroPlus, PKSIM and Simcyp. It is a good tool for evaluating and optimizing clinical trial design to select the dose and dose schedule. It can also be applied as an alternative to DDI trials in some special populations [16] such as pediatric population, pregnant women, elderly people and organ impairment populations.

The aim of the paper [17] is to introduce fundamental concepts of PBPK /PD modeling. It Illustrates basic steps in PBPK model building. The PBPK model for ciprofloxacin was constructed using Pksim software. The therapeutic effect of 100mg once-daily and 500mg twice daily of CIP was simulated for bacterial strain. In conclusion, PBPK models can be a valuable support in drug development, in particular considering the possibility to generate a priori simulations. As a consequence, they are increasingly used in pharmaceutical companies and regulatory agencies like the US Food and Drug Administration [17].

In the study conducted by Olivares-Morales et.al, [18] oxy’s bioavailability differences were investigated by means of PBPK modelling and simulation approach combining in vivo, invitro and in silico data with extended version of MSAT model [18] using NONMEM and Matlab platform. This Model comprised of two systemic blood liver compartments, three empirical tissue compartments. The estimated bioavailability was found to be 5.94% whereas reported bioavailability was found to be 6.2± 1.2%. It was observed that the model slightly overestimated relative bioavailability.

1.6 Physiology-based pharmacokinetics of caspofungin

In this paper [19] they have developed and validated physiology-based pharmacokinetics (PBPK) model to predict pharmacokinetics in pediatrics. The PBPK model was built and validated with raw data of clinical trials [19]. Model was scaled for pediatric patients. Simulated results of PBPK model were in good agreement with observed values. The founded PBPK model of CAS without individualized parameter was able to predict the pharmacokinetics in different patient population correctly [19].

The paper [20], introduce the concept of physiologically based pharmacokinetic (PBPK) modelling and provides some background on PBPK models and their data requirements, introduces strategies for PBPK modeling in drug development. The model was simulated using PKSIM software. The PBPK model and assumptions were initially validated in rats, dogs and humans following i.v. and oral administration [3]. The PBPK model was able to accurately capture the observed oral plasma concentration–time profile [20] indicating the assumption of passive absorption is valid for this compound. Using the predicted absorption and clearance,
the bioavailability was accurately estimated. It was concluded that the use of PBPK model maximize the clinical potential of drugs which was accepted by the pharmaceutical industry and regulatory agencies [20].

The paper [21] demonstrated the methodology, application and limitation of PBPK modeling. The Primary result of simulation was set of concentration time curves, illustrate temporal behavior of drug in blood/plasma and or other organ. The software used for simulating the model Matlab, Model maker, Berkeley Madonna, PK-sim, Simcyp and Gastroplus. The application of PBPK model was predicting of drug pharmacokinetics in individual with disease/altered physiology/pediatric population. The author concluded that the simulation of PBPK models are developed to explore effect of various factors on drug pharmacokinetics [21].

In the paper [22] they have estimated the target dose or biologically effective dose. These compartment partitioning model of fish was used to predict the toxicity in fish. For specific activity compounds simple partitioning models are not sufficient. PBPK modelling is a strong tool for extrapolation among different exposure routes and different species [22].

CONCLUSION

In summary, these papers argued that in the pharmaceutical industry, PBPK modelling is used for purposes, such as mechanistic studies, aiding internal drug discovery or clinical development decisions, and informing regulatory communication including filing at various stages. PBPK model is an effective model in simulation and determination of pharmacokinetic parameters. A substance will only take effect if it can be absorbed by the body, so bioavailability is the key to creating a supplement that delivers proven benefits. Bioavailability is a measure of how easily a substance can be absorbed by the body. So, estimation of bioavailability using PBPK model helps in predicting the dosage for a special population.

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