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PBPK MODELLING FOR PREDICTION OF DRUG -DRUG INTERACTION

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ABSTRACT
In modern pharmaceuticals, Physiologically Based Pharmacokinetic (PBPK) modelling has emerged an essential technique used in the estimation of drug - drug interaction. The technique incorporates physiological, biochemical, and pharmacological informations to know the pharmacokinetics of the drugs in a virtual physiological system. It offers a superior alternative compared to other pharmacokinetic modeling techniques. There is an increasing use of PBPK models in estimating DDI, as it allows evaluation of how a drug interacts with the body in the absorption, metabolism, and elimination of other drugs. Such predictions enhance drug safety and optimize drug dosage without requiring many experiments. Pharmacokinetic models are currently supported by several software like Simcyp, GastroPlus, and PK-Sim, among others, and this has made PBPK modeling more accepted in regulatory processes during drug approvals. Still, there are various limitations associated with PBPK modeling such as lack of accurate data.

KEYWORDS: PBPK Modelling, Drug - Drug Interaction.

INTRODUCTION

Physiologically-Based Pharmacokinetic (PBPK) Modelling has turned out to be a very effective and mechanism-based tool to predict ADME of drugs in humans as well as animals. The main difference between PBPK and conventional PK models is that PBPK models use detailed physiological, biochemical, and specific information about the drug, whereas the latter does not have any of these elements in their structure. Anatomical compartments connected by bloodstream constitute the basis for creating these models.[1,2] Within the past few years, the use of PBPK modeling in the field of pharmaceutics and regulation science has been highly popular owing to its capability in predicting pharmacokinetic responses in special patient populations such as children, elderly, and those with organ impairments. Furthermore, PBPK models are key players in the process of dose optimization and first-in-man studies.[3,4]

One of the major areas of application for PBPK modeling is the estimation of drug - drug interaction. With use of enzyme kinetic, transporter, and physiological variation, the effects of multiple drugs taken together on systemic concentrations can be quantitatively evaluated using PBPK. PBPK is especially useful for drugs that undergo metabolism via cytochrome P450 enzymes.[5,6] One of the applications of PBPK models is determining the interactions between various drugs in terms of concentration levels. Through enzyme kinetics, transporters, and physiological parameters, the interaction between several drugs when administered can be quantified using PBPK modeling. PBPK models are particularly suitable for determining the interactions for drugs that go through metabolic processes involving cytochrome P450 enzymes.[7] The development in computational methods and the generation in vitro and in vivo data has helped development of PBPK models as a crucial element in model informed drug development (MIDD).

Their use alongside other modeling techniques helps improve decision making, minimize the extent of conducting clinical trials, and expedite drug development efforts.[8]

Drug–Drug Interaction

Definition of Drug Interaction (DI) Drug interaction occurs when the effect on a particular drug is changed by administration of another drug at same time. The consequences of drug interactions may be positive in that therapeutic effect is improved or they could be negative such that they cause adverse drug reactions or even toxicity. Knowledge of drug interactions is necessary to ensure drug safety.[9] DDIs are generally divided into three types: pharmacokinetic interactions, pharmacodynamic interactions, and pharmaceutical interactions. Pharmacokinetic interaction deals with modification of ADME properties of a medication. For example, an inhibitor or inducer of drug-metaboliz enzyme like Cytochrome P450 enzymes can greatly influence drug plasma concentration.[10]

Pharmacodynamics is described as an interaction between two or more drugs that act on the same physiological target. The combination of two central nervous system depressants can lead to an increased level of sedation.[11] Pharmaceutical interactions (also known as physicochemical interactions) occur before drug administration, typically when drugs are mixed together, leading to incompatibility or reduced stability.[12] DDIs have great clinical importance as they may cause therapy failure or toxicity. Some factors that affect DDIs include individual patient characteristics like age, genetic polymorphism, disease state, and multiple drug intake.[13]

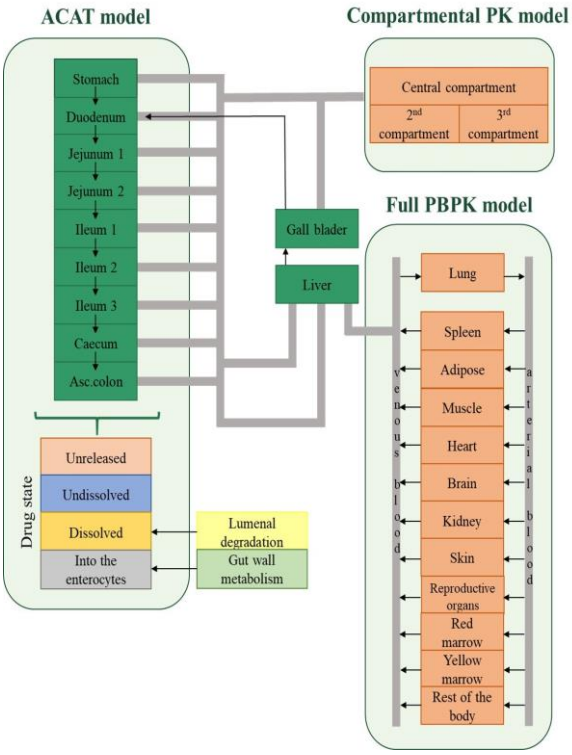
Therefore, it can be considered essential that prediction and evaluation of DDIs plays an important roles during drug development. The methods used to predict drug interaction is Physiologically Based Pharmacokinetic (PBPK) Modeling.[14]

Software and Tools Used in PBPK Modeling

Physiological Based Pharmacokinetic (PBPK) Modeling is highly dependent on software packages that make use of computational models to capture information from physiology and biochemistry in order to create a virtual population model for pharmacokinetics studies. A number of software packages both commercial and non-commercial have been successfully employed for PBPK and DDI modeling.[15] A popularly used commercial platform is the Simcyp PBPK Simulator offered by Certara. This is an integrated platform that offers a complete solution to PBPK models for the prediction of pharmacokinetics, determination of optimal dosing, and evaluation of DDIs. This model includes in vivo and in vitro information in addition to being applicable to a wide range of populations[16] Other commercial tools include GastroPlus software that is especially used for mechanisms of drug absorption and PBPK analysis. This program has various models including the ACAT model and enables prediction of absorption, bioavailability, and pharmacokinetics of drugs via various routes of administration.[17] Along with the proprietary software, there are many free programs available such as PK-Sim along with another program called MoBi that serves as a complement to it.

PK-Sim performs whole-body PBPK simulations with the integration of physiological characteristics of both humans and non-human subjects. The program can use data related to the level of genes and thus predict the activities of enzymes and transporters, making it a more advanced tool.[18] The most common other tools include NONMEM, Phoenix WinNonlin, Monolix, and Phoenix NLME, which are employed for PK/PD analysis.[18]

These Software applications become integral part of discovery in contemporary times through in silico methods to predict pharmacokinetics, optimize doses, perform virtual clinical trials, and evaluate drug-drug interactions in order to minimize animal tests.[19]



Regulatory Perspective of PBPK Modelling

The Physiologically-Based Pharmacokinetic (PBPK) model has been widely recognized an important tool in aiding drug development and designing clinical trials within regulatory authorities worldwide. The U.S. Food and Drug administration, European Medicines Agency, and Pharmaceuticals and Medical Devices Agency have published various guideline concerning utilization of PBPK models in their respective regulatory submission processes.

PBPK models have found increased utility in predicting pharmacokinetics in special population groups such as pediatrics, geriatrics, and individuals suffering from organ dysfunction. PBPK modeling involves incorporation of physiological and biochemical properties of a system, along with pharmacological

properties of a compound, into mathematical modeling equations, which enable predictions beyond the realm of observations obtained from clinical trials.[20] Guidance on the reporting of PBPK models by the FDA emphasizes the importance of model validation and verification. The FDA recommends a step-by-step approach, whereby the process involves model development, model qualification by using clinical data and sensitivity analysis. PBPK modeling is highly regarded for prediction of cytochrome p450-dependent drug-drug interactions in particular interactions involving CYP3A4 and CYP2D6 enzymes.[21] In the same vein, the European Medicines Agency endorses the application of PBPK modeling approaches within the context of regulatory submissions, especially in DDI assessment and pediatric extrapolations. The guidelines issued by EMA stress the need to focus on model credibility through the adoption of validated software platforms like Simcyp and GastroPlus, among others.[22] The Pharmaceutical and Medical Devices Agency also acknowledges the use of PBPK modeling as an effective method for bridging studies and ethnic sensitivity analysis. The PMDA advises sponsors to conduct discussions concerning their assumptions, parameter choice, and application early on.[23]

PBPK modeling is now being approved for use in other areas, such as biowaiver, formulation modification, and transporters' interaction studies. But there is the need for clear documentation, including the PBPK model structure, data source, assumptions made during model development, and the level of uncertainty in the study.[24]

Though there are many advantages, some of the issues faced while trying to gain regulatory approval of PBPK models include the complexity of models, variability of input parameters, and lack of validation for some categories of drugs. Hence, there must be an ongoing cooperation between all stakeholders involved in these processes.[25]

Comparison of PBPK Modeling Software

Software	Developer	Type	Key Features	Applications
Simcyp Simulator	Certara	Commercial	Population-based PBPK, DDI prediction, virtual trials	Regulatory submissions, dose optimization
GastroPlus	Simulations Plus	Commercial	Advanced absorption (ACAT model), oral PK prediction	Bioavailability, formulation development
PK-Sim	Open Systems Pharmacology	Open-source	Whole-body PBPK, enzyme/transporter integration	Mechanistic modeling, academic research

Studies for the prediction of drug - drug interaction

The model adequately simulated the time-dependent inhibitions effect and sensitivity to CYP3A4 of flumatinib, offering mechanistic information regarding the drug-drug interactions caused by flumatinib. The findings provide an opportunity for dose optimization and risk management for patients with chronic myeloid leukemia when concomitantly receiving other drugs that interact with CYP3A4 activity. Therefore, this work underlines the effectiveness of the use of PBPK model to predict DDIs and guide treatment of patients with oncology medicines.

Additional clinical research will be conducted to confirm these predictions and fine-tune dosing guidelines.[26]

Group A subjects received both fluconazole and ainuovirine, resulting in increased geometric means of ainuovirine Cmax,ss and AUC0–24,ss up to 233.0% and 349.6%, respectively, compared with ainuovirine alone.

For group B, no influence of ainuovirine on Cmax, ss, AUC0–24,ss and Tmax,ss for fluconazole. No deaths and grade ≥3 serious adverse events occurred. The simulation ability of the PBPK model for predicting ainuovirine-fluconazole DDI was outstanding, since the ratios of predicted to observed values were near to 1.0.

Coadministration of ainuovirine with fluconazole substantially affected the PK parameters of ainuovirine but not vice versa. This DDI model demonstrates that dose adjustment is required for coadministration of ainuovirine and fluconazole.[27]

The established PBPK model correctly predicts the pharmacokinetics of each drug. Daruavir/ritonavr had increased Cmax of ibrutnib, zanubrutnib, and acalabrutnib by 496%, 312%, and 160%, respectively.

Efavirenz decreased Cmax by 43%, 33%, and 37%, respectively, while etravrine produced smaller reductions in Cmax by 5%, 0%, and 10%. The recommendations for dosing based on the predictions are as follows: with the co-administration of ibrutnib, zanubrutnib, and acalabrutnib with daruavir/ritonavir, the dosages should be 105 mg, 40 mg, and 50 mg twice daily, respectively; with the administration of these drugs in combination with efavirenz, their dosages should be 980 mg, 240 mg, and 150 mg twice daily, respectively.dose not adjust with etravrine. Conclusion: PBPK models have correctly predicted the pharmacokinetic characteristics of ibrutinib, zanubrutinib, acalabrutinib, and those of the anti-retroviral, daruavir/ritonavir, efavirnz, and etravirne.[28]

The validated models showed a potential increase in exposure to total cariprazine by up to 6.0-, 2.9-, and 1.1-fold with co-administration of strong, moderate, and weak CYP3A4 inhibitor, respective, during steady state.

The PBPK model facilitated more appropriate dose adjustment of cariprazine during short-term and long-term co-administration of strong and moderate CYP3A4 inhibitor. Results from these models facilitated an update of the prescribing information in the United States in November 2024 for providing guidance on appropriate dose adjustment of cariprazine when used concomitantly with CYP3A inhibitors. The goal of these updates was to maintain the therapeutic effect of cariprazine while reducing its side effects.[29]

The model was successful in representing plasma concentration-time data described for various studies ranging from preclinical and clinical. All human data points used in fitting the model were within the 95th percentiles of the prediction, and PK parameters remained within two fold of the observe data. In studies involving the effect of food on drug disposition and drug interaction involving itraconazole and esomeprazole,single dose of ARV-110 was administered, where predicted vs. observed AUC 0-inf were 13563.0 vs. 7646.0 ng.h/ml, 4358.0 vs. 4618.3 ng.h/ml and 1919.0 vs. 1403.3 ng.h/ml in high fat, moderate fat, and low fat condition.[30]

Thirty-eight out of the total drugs registered in Japan included PBPK modeling, most of which were in connection with drug-drug interaction. When the data were compared with Europe, none was found completely identical, but there were partial similarities with only seven drugs. On the other hand, when the data were compared with the US, there were two completely identical drugs and partial similarities with twenty-four drugs. The comparison of the specific details of the twenty-four drugs that were partially similar indicated the tendency for the Japanese package insert to be detailed.

There is an increasing significance for PBPK model analysis in current drug development, especially for Japan where detail is favored in package inserts.[31]

The cryopreserved human hepatocyte in culture exhibit low sensitivity to induction of cytochrome P450s 2C and uridine 5' diphospho glucuronosyltransferase, which makes in vitro-in vivo translation difficult for the DDIs potential.

The present work validates that TruVivo is an appropriate model to be used in vitro. Through the physiologically- based pharmacokinetic modelling approach, assessed the role of induction parameter on prediction accuracy, proving that Truvivo can be employed as good tool for cytochrome P450s 2C and uridine 5' diphospho glucuronosyltransferase risk evaluation.[32]

The simulated DDI effect by PBPK models of standard dose rifampin on linezolid was well correlated with experimental DDI ratio of AUC and Cmax ratio of 0.77 and 0.87, respectively. Based on PBPK simulation results, ABCG2 and ABCB1 were responsible for linezolid/rifampin DDI, but ABCB1 was mainly involved in the interaction.

Administration of rifampin at increased dose ranging from 20 to 40 mg/kg/d led to exposure of linezolid being comparable to that of rifampin at a regular dose of 10 mg/kg/d. Conclusion: This study demonstrated that ABCB1 transporter was primarily associated with the drug interaction between rifampin and linezolid.[33]

There is a high correlation between the predicted DDI effects of rifampin at a standard dose level through PBPK models and experimentally determined DDI ratios of AUC and Cmax of 0.77 and 0.87, respectively.

According to the PBPK modeling data, ABCG2 and ABCB1 are involved in the DDI effect between linezolid and rifampin; however, ABCB1 plays a more important role in this effect. Linezolid exposure at increased rifampin dosage levels ranging between 20 and 40 mg/kg/d equals that of rifampin dosage at a normal level of 10 mg/kg/d. Conclusion: In this study, ABCB1 transport protein was found to play important role in rifampin/linezolid drug interactions.[34]

The PBPK model verified that the drug had minimal risk for DDI as a precipitating agent in the majority of in vitro tested drug metabolize enzyme and transporters.

Niraparib, in vitro, does not have CYP inhibitions, causes induction of CYP1A2 and not of CYP3A4 and is not CYP substrates, while PARPi's have various inhibition and induction of several enzyme/transporters and themselves undergo CYP metabolism. However, doses of niraparb $\geq$ 200 mg , weak induction is expected with sensitive substrate for CYP1A2 like caffeine and, along with olaparib, increased serum creatinie levels in cancer patient, while moderate inhibition may be expected through MATE-1/-2K substrate, including metformen, by a PBPK model of niraprib without a dedicated DDI study.[35]

Physiologically-based pharmacokinetics (PBPK) / permeability-limited multicompartment liver (PerMCL) approach, considering zonal transporters and enzymes involved in drug metabolism. Simulations of systemic and intrahepatic concentrations of pravastiatin, rosuvastiatin, and atorvastiatin were done for Healthy Volunteers (HV), Obese, and MASH populations with Simcyp simulator. Then, pharmacodynamics model constructed with Simcyp was used for simulating effects of changes in the cholesterol lowering efficacy of rosuvastatin in different populations. The transport and metabolic processes in liver were validated using clinical data. Organic anion transporting polypeptide (OATP)1B genetic information.[36]

The PBPK models for CLB, N-CLB, and STP accurately captured observed pharmacokinetics in healthy adult subjects and pediatric patients aged greater than two years old. Comparison of the model results with existing DDI studies demonstrated a clinically inconsequential change in CLB exposure following co-administration with STP (Cmin ratio = 1.77). However, exposure to N-CLB increased up to sevenfold among extensive CYP2C19 metabolizers (Cmin ratio ~7) and decreased slightly in poor metabolizers (Cmin ratio = 0.9), which corresponds to N-CLB's dependence on CYP2C19 activity. Predicted exposures to CLB, N-CLB, and STP in pediatric patients younger than two years old were similar to those obtained in older children and were within their therapeutic ranges.[37]

PBPK model have been developed to predict effects of CYP3A4 mediated DDIs in EE. The clinical study has shown the elevation of EE exposure after co-administration with the SULT1E1 inhibitor etoricoxib/ziritaxestat, which necessitated the expansion of the PBPK model to provide prediction of SULT1E1 mediated DDIs. The PBPK model with SULT metabolism included was constructed and the interaction was simulated between the PBPK models created for EE, etoricoxib and ziritaxestat. EE exposure was within the simulated 95th percentile in both the control and DDI groups. The simulated ratios for Cmax and AUCt were within 1.5-fold from the measured data. Simulations indicated that clinically significant DDIs cannot be anticipated upon the co-administration of 120 mg etoricoxib or 35 µg EE; however, significant DDIs can be expected when 600 mg ziritaxestat or 35 µg EE is co-administered. Simulation predicted that a 35 µg dose of EE would generate similar EE exposure as that of 20 µg EE when it is co-administered with ziritaxestat.[38]

Pirtobrutinib physiologically based pharmacokinetic (PBPK) modelling was performed based on physicochemical data, in vitro findings, and clinical pharmacology studies result. The PBPK models could predict the interaction potential with itraconzole, rifampcin, and midazolem as the clinically observed interactions with pirtobrutinib, with estimated pirtobrutinib and midazolem AUC ratio in 0.91- to 1.16-fold range as compared with the clinical observation.

The PBPK model predicted a 1.20- to 1.73-fold increase in the pirtobrutenib AUC under the strong and moderate CYP3A4 inhibitors. Also, the AUC ratios of pirtobrutenib estimated by the PBPK model under the mild and weak CYP3A4 inducers were in the range of 0.51- to 0.86-fold. Thus, combined with exposure-response relationship of safety and efficacy for the treatment of hematological cancers, the CYP3A4 modulation.[39]

Physiologically Based Pharmacokinetic (PBPK) modelling approach used for investigate combination therapy tamoxifen and estradiol in breast cancer patients with osteoporosis risk. GastroPlus® software was employed to create the validated PBPK models for both compounds, based on the available information concerning their physicochemical properties and kinetics, as well as ADMET Predictor® generated estimations for the data lacking in literature. Both physiological and clinical scenarios were assessed for possible drug interaction induced via CYP3A4 enzymes.

Comparative analysis of the pharmacokinetic parameters (F, Cmax, Tmax, AUC) has shown that there is an excellent correspondence between experimental and predicted values of less than twofold prediction error.

Drug interaction simulation performed in both dynamic and static models demonstrated that tamoxifen's pharmacokinetics are not affected by estradiol, regardless of its dosage and virtual population size.[40]

PBPK modeling represents a distinct paradigm to improve MIDD and MIPD. Nonetheless, current use of PBPK modeling remains confined to drug pharmacokinetics, with no inclusion of either efficacy or safety parameters. This approach prevents us from realizing the true potentials of PBPK modeling. In our study, we have combined PBPK modeling along with QSP and toxicology to estimate the risks associated with DGIs, DDIs, and impaired renal function through simultaneous estimation of pharmacokinetics, pharmacodynamics, and myotoxicity risks that were different from plasma exposure.[41]

In vitro and clinical PK data are used to develop physiologically based pharmacokinetic (PBPK) model to predict the effect on CYP3A and P- gp modulator on the PK of valemetostat. The PBPK model developed was validated using clinical drug–drug interaction (DDI) data with a mild CYP3A inhibitors (flucoinazole), a strong CYP3A/P- gp dual inhibtor (itracoinazole), and strong CYP3A/P- gp dual inducer (rifampicin). It was shown from the validation that the contribution of CYP3A and P- gp in the gut or liver to valemetostat PK captured correctly in PBPK model. With the validated PBPK model, we further investigated the effects of either a CYP3A or a P- gp inhibitor, or a moderate CYP3A inducer on valemetostat PK. From the results obtained, it is shown that the PBPK model with contribution of CYP3A and P- gp in the gut and liver was able to predict the effect of CYP3A/P- gp modulator on valemetostat PK accurately.[42]

The in vitro and clinical PK data was applied to build the PBPK model that predicts the influence the CYP3A and P-gp inhibitors/inducers of the PK of valemetostat. The PBPK model built was evaluated through comparison with the clinical DDI data with a mild CYP3A inhibitor (fluconazole), high CYP3A/P-gp dual inhibitor (itracoinazole), and strong CYP3A/P-gp dual inducer (rifampicin). It was seen from the evaluation of the PBPK model with the above data that the contribution of

the CYP3A and P-gp enzymes in the gut and liver for valemetostat PK were well-represented in the PBPK model. Using the evaluated PBPK model, we investigated the effects on the valemetostat PK by the CYP3A or P-gp inhibitor, and moderate CYP3A inducer, respectively. The outcomes of the investigations showed that the evaluated PBPK model was able to predict the effects of CYP3A/P-gp modulators on valemetostat PK.[43]

PBPK modelling approach applied to investigate Teliso-V drug–drug interactions (DDI) potential. The previously published PBPK model of MMAE, on major metabolite, and newly develop PBPK model for telisotuzumab were employed to build a novel PBPK models of Teliso-V.

The PBPK model was built by simulating the release of unconjugated MMAE with drug-to-antibody-ratio-dependent the impact of the co-administration of ketoconazole and rifampin, the strong inhibitors/inducers of CYP3A4 enzyme, respectively, on the pharmacokinetics of Teliso-V was assessed. A 43% increase and 70% decrease in MMAE AUC are predicted upon co-administration of Teliso-V with kitoconazole and rifampicn, respectively. DDI magnitude was similar to the one observed btw another approved antibody-drug conjugate (ADC), containing MMAE, and ketoconazole and rifampicn. The currently performed PBPK analysis revealed no effect of Teliso-V on the pharmacokinetics of midazolem, the probe for CYP3A enzymes activity.[44]

An iclepertin PBPK model was constructed and qualified based on physicochemical, in vitro, and Phase I clinical studies in which iclepertin was studied by employing different drug administration routes, different formulations, varying dose sizes, administration of single/multiple doses, and varying fasting/food states.

Additionally, the model was qualified for its application on simulating the DDI studies involving iclepertin with a potent inducer of CYP3A4 activity (rifampicin) and a potent inhibitor of CYP3A4 activity (itraconazole). The DDI simulations of iclepertin (10 mg/day) as a victim/perpetrator drug were conducted based on the qualified model. With adequate qualification using clinical DDI data, the model was considered qualified for predicting novel clinical situations, including varying drug doses, co-administration of other drugs being different CYP3A4 substrates, weak–moderate inducers or inhibitors of CYP3A4, and even poly-medication situations in vivo.[45]

The parameters used in PBPK modeling use the method of parameter optimization based on Phase I data. But this contradicts the bottom-up approach of predicting human pharmacokinetics through pre-clinical experiments before conducting any human trials. In this paper, we solve the problem by incorporating a new metabolic rate function in our PBPK model. The major difference between the MM rate equation and the modified equation lies in the fact that the latter equation is applicable even when ET = KM. From our findings, it can be shown that the usage of the modified metabolic equation provides better results compared to the classical MM metabolic rate equation even in dynamic PBPK modeling. Thus, in light of these findings, we suggest new guidelines which will help in applying the modified metabolic rate equation in various PBPK models.[46]

The model was develop based on PK data following single dose in healthy volunteers. Translational potential of the model was demonstrated by its ability to predict riluzole PK in patients with amyotrophic lateral sclerosis, spinal muscular atrophy, older adults, renal impairment, hepatic impairment, and in presence of a high-fat meal.

Relative roles of CYP1A1 and CYP1A2 in the metabolism of riluzole were confirmed by predictions of drug-drug interaction between riluzole and fluvoxamine, which is a potent CYP1A2 inhibitor and poor inhibitor of CYP1A1, in pediatric patients with obsessive-compulsive disorder. In conclusion, CYP1A1 appears to be a main enzyme involved in metabolism of riluzole, while CYP1A2 plays a similar role. Only those clinically relevant inhibitors for both enzymes need to be considered for safety issue when concomitantly administering the drug. Potent inhibitors for both CYP1A1 and CYP1A2 may be taken cautiously only if they have little effect on the activity of each other. It would be better to avoid concomitant administration of CYP1A1 inducer if possible. Further evaluation of the role of enzymes involved in riluzole metabolism needs to be done after completion of drug-drug interactions study.[47]

The developed model precisely simulated the pharmacokinetics of RSV in the Caucasian, Chinese, Malay, Japanese, and Korean cohorts. The model was also able to simulate the conversion from RSV to RSV lactone, pharmacokinetic change of RSV associated with OATP1B1 and BCRP genetic variants, and drug-drug interaction with rifampin and cyclosporine. Based on sensitivity analyses, it was identified that decreased OATP1B1 activity in liver or increased BCRP efflux transporter in intestine are possible causes of pharmacokinetic changes observed during the third trimester of pregnancy. In contrast to the previously published models, our model considers many factors such as genetic polymorphism, ethnicity differences, metabolism to lactone form, DDI, and pregnancy.[48]

Into the two modeling approaches of population pharmacokinetic (PopPK) and physiologically based pharmacokinetic (PBPK). The gastric emptying delay (GED) due to the administration of dulaglutide was assessed on healthy volunteer and in patients by T2DM at different dose strengths of dulaglutides. The proposed modeling approach was validated in its ability to reproduce the observed GED-related DDIs for lower doses of dulaglutide, as well as to predict DDIs for the

higher (4.5 mg) dulaglutide dose. In clinical studies, it was found that 1.5 mg dose of dulaglutide has not clinically significant influence on the pharmacokinetics of small molecules. Modelling showed similar results for the 4.5 mg dose of dulaglutides.[49]

For the prediction of the magnitude of TDI in the case of DDI with mechanistic static modeling (MSM), the following optimum values for incubation were found: pre- incubation duration of 40 min precipitant and an incubations duration of 10 min in case of CYP3A4 substrate, midazolem (10 μM) concentration 0.1 mg/mL HLM. The problem of overestimation of the DDI magnitude by MSM persisted (AFE = 4.83, AAFE = 4.87) despite the application of the parameters obtained during the optimization of the incubation process.

However, using these optimum incubation values improved the prediction results in the case of physiologically-based pharmacokinetic (PBPK) model, which resulted in AFE = 1.94 and AAFE = 2.13.

Moreover, 60% of predictions fell into the twofold range.[50]

All PBPK-simulated changes in the plasma concentrations of dordaviprone when coadministered with moderate (erythromycin, fluconazole), weak (cimetidine) inhibitors, and moderate (efavirenz), strong (rifampicin) inducers of CYP3A4 were in agreement with their CYP3A4 potency levels (AUC ratio = 2.68, 2.48, 1.42, 0.35, and 0.17, respectively). In PBPK simulations, no changes were observed in the simulated AUC and Cmax of the probe drugs for CYP3A4 (midazolam), CYP2C8 (repaglinide), and CYP2D6 (desipramine) when coadministered with 625 mg dordaviprone compared with their values in the absence of dordaviprone (AUC ratio = 1.0). This value did not change in the sensitivity analysis with 10-fold more potent inhibition constant values.[51]

Simulation results also indicated that there is a ~30% increase in the exposure to unconjugated AF-HPA after the administration of 36 mg/m2 by IV route in the presence of itraconazole, which is known to inhibit CYP3A4 and P-gp enzymes. A minimal effect on the exposure to unconjugated AF-HPA was seen in patients having mild hepatic impairment, and this result is consistent with the clinical observations. There is expected to be a ~1.5-fold increase in the exposure to unconjugated AF-HPA on patients with mild to severe hepatic impairment. Finally, the current PBPK model may be used for the prediction of DDI and hepatic impairment in other ADCs using the same linker-payload combination.[52]

The existing PBPK model of adults with respect to crizotinib was extrapolated to the pediatric population using a different ontogeny of CYP3A4 to evaluate the PK parameters after administration of a single oral dose of crizotinib in pediatric subjects of age 1 to 6 years. The same model was used for conducting a BE study involving ICV%. For adult population, estimatgeometric mean ratios for AUC inf and Cmax for oral solution (OS) versus granules formulation was 98.33 and 89.94, respective, with probability of demonstrate BE in adults as 100% for AUC inf and 90.3% for Cmax.[53]

In this study, it was shown that major cannabinoids along with their respective metabolites present in the plasma samples obtained from the cannabis users inhibit the in vitro metabolism of hydromorphone using UGT2B7 enzyme. In addition to this, there is a possibility of the in vivo inhibition of hydromorphone metabolism by cannabinoids and their respective metabolites which results in the possible interaction between drugs if used simultaneously.[54]

DII models were developed and validated through simulations carried out via the Simcyp simulator and experimental work conducted in vitro. Optimization of the drug's dose regimen was done via the use of the developed DDI models.

There was no relationship found between ISA and either high or low blood pressure. Hypertension caused by the inhibition of CYP3A4 enzyme was frequently associated with amlodipine and nifedipine. In silico predictions indicated that ISA doubled the plasma concentration of nifedipine IR and CR, increased its maximum concentration by 1.51 and 2.15 folds, and increased the maximum reduction in systolic blood pressure by 3.5 to 4.09 folds in nifedipine IR. The impact of amlodipine on nifedipine was insignificant. Dose optimization, including reduction in the dosage of nifedipine.[55]

(PBPK) models that simulates the coadministration and washouts DDIs between posconazole DRT and victim drugs (ranolazine and lurasidone) in healthy normal-weight subjects and obese patients. two main results obtained from this model are 1) substantially increased when the BMI was equal to or greater than 35 kg/m2 and 2) the process of CYP3A4 enzyme inhibition by posaconazole is irreversible. The PBPK model can be used in future for evaluation of the washout DDIs between posaconazole and CYP3A4 substrates in normal-weight patients and obese subjects.[56]

Advantages of PBPK Software Tools

PBPK models are computational software packages which allow for the mechanistic simulation of pharmacokinetics via integration of physiological, biochemical, and drug-related factors. PBPK models allow prediction of drug exposure in special populations like pediatric and geriatric patients or those with organ dysfunction.[57]

One of the biggest advantages of the use of these modeling and simulation tools is that they enable virtual DDIs. In recent times, more and more regulatory

agencies, including the U.S. Food and Drug administration and the European medicine Agency, are accepting use of PBPK modeling data in their regulatory reviews.[58]

Further, Physiologically Based Pharmacokinetics Modeling (PBPK) helps carry out in silico experiments, which allows for the optimization of dosage, pharmacokinetic variation prediction, and minimization of costs incurred during drug discovery processes.[59]

Limitations of PBPK Software Tools

However, PBPK models come with several drawbacks. For instance, the predictive capacity of PBPK models heavily relies on the input data available to inform the models. Inaccurate or incomplete data might affect the performance of the model negatively. Furthermore, developing and validating PBPK models are quite demanding in terms of skills and knowledge, requiring proficiency in pharmacokinetic modeling. The complexity associated with these models, together with the expensive cost of using some proprietary software packages, may limit the use of PBPK models. Lastly, PBPK models are less accurate when dealing with biological events with nonlinear pharmacokinetics or new modes of action.[60]

CONCLUSION

Physiologically Based Pharmacokinetic (PBPK) modelling has become tool in modern drug development, providing a mechanistic approach to predict drug behavior, optimize dosing strategies, and evaluate drug–drug interactions (DDIs).

By integrating physiological, biochemical, and drug-specific data, PBPK models enhance the understanding of pharmacokinetics across different populations and clinical conditions. The increasing acceptance of PBPK modeling by regulatory authority such as the U.S. Food and Drug Administration and the European Medicines Agency highlights its importance in regulatory decision-making, including dose selection and safety assessment.

Despite challenges related to data availability, model complexity, and the need for specialized expertise, continuous advancements in computational tools and biological data are improving the reliability and applicability of these models. Overall, PBPK modeling holds significant promise for enhancing drug development efficiency, reducing reliance on extensive clinical studies, and supporting the advancement of precision medicine through better prediction of complex pharmacokinetic behaviors and drug interactions.

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