Review Article

PHARMACOKINETIC/PHARMACODYNAMIC (PK/PD) MODELING: AN INVESTIGATIONAL TOOL FOR DRUG DEVELOPMENT

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ABSTRACT

Pharmacokinetic-Pharmacodynamic (PK/PD) modeling is scientific mathematical tool which integrates relationship PK model (describing the relationship between dose, systemic drug concentrations, and time) to that of PD model (describing the relationship between systemic drug concentration and the effect vs time profile) and a statistical model (particularly, the intra- and inter-individual variability of PK and/or PD origin). PK/PD approach is used from initial preclinical stage to last clinical phases for exploring the concentration-effect relationships executed using various approaches, such as steady state concentrations versus non-steady state concentrations models and parametric versus nonparametric models. Basing on the concentration-response invariant data basic models such as fixed-effect, linear, log-linear, E_{max} and sigmoid E_{max} models are used. But in case of time-concentration and time-response variant conditions effect compartment, acute tolerance, sensitization and physiological indirect response models have been used. Once data collected suitable model is identified and validated then predictions about the efficacy and safety of the dosage form and dose. PK/PD modeling can be used as an applied science tool to provide answers on efficacy and safety of new drugs faster and at a lower cost. PK/PD modeling has a different type of applications in various fields of therapeutics like anti-infective areas, anticancer, analgesic, and anti-inflammatory and in CNS pharmacology like antipsychotic areas. Variations in the same species in terms of response (PD) is simply depends upon the pharmacokinetic (PK) constraints. These variations can be predicted and evaluated. At this stage PK/PD concepts can be applied to individual dose optimization by population PK/PD models. The limits of PK/PD approaches include the development of appropriate models, the validity of surrogate endpoints, and the acceptance of these models in a regulatory environment.

Keywords: Pharmacokinetics (PK), Pharmacodynamics (PD), Fixed effect, *Emax* model, Sigmoidal *Emax* model, Log-linear, Physiological indirect model, Population PK/PD model.

INTRODUCTION

Pharmacokinetics (PK) describes the quantitative relationship of concentration-time profiles in different body fluids (plasma, blood, urine, saliva and cerebral spinal fluid (CSF), etc). Phamacodynamics (PD) quantifies the effects relates to the intensity of the effects and the concentration present at the hypothetical effect site. It studies what the drug does to the body. In past days the correlation between PK/PD was done to extract the useful data in relation to predict the dose, effects, desired dosing rate, and time. But sometimes there will be divergence between drug concentrations (PK) and PD response. The varying PD response is due to some of the factors like PK process, signal transduction, secondary post-receptor modifications and sometimes due to variability with in the study population. This led to development of another new technique this is called as pharmacokinetics (PK) - pharmacodynamics (PD) modeling, which integrates and correlate between concentration (PK) and effect (PD).

PK/PD modeling is a mathematical description of the relationship between pharmacokinetics (PK) and pharmacodynamics (PD)[1]. This technique changed estimation of PK/PD parameters, its changes as drug intake and other clinically relevant variables. To measure pharmacological effects bio-mathematical models are developed to characterize and evaluate pharmacodynamic (PD) actions. These bio-mathematical models are the simplified forms of the phenomenon described in terms of an algebraic or differential equations. This PK/PD modeling not only describe, but also foretell about the distinct situations like allometric scaling (preclinical to clinical extrapolations), multiple dosing schemes (different dosages or routes of administrations)[1]. Presently there is growing importance to this technique in the drug development.

This innovative technique that utilized in all of drug development stages, this will help to draw the dose-response curve for onset, magnitude and duration of effect. PK/PD simulation allow the assessment of the descriptive parameters as function of dose and dose rate, also helps in optimizing dose and dosing regimens[1].

Role of PK/PD modeling

Now-a-days PK/PD modeling has a significant increasing role in all phases of drug development (Table I) i.e., early clinical discovery stage to late drug development stages to improve the efficiency and quality of decision making[2,5].

In preclinical stages, PK/PD used in toxicokinetic studies of various chemical entities[6] and extrapolation of results from animals to humans (allometric scaling) via physiological modeling[7]. In phase 1 study, enable crucial decisions (e.g.: go/ no go) safety and tolerability of compounds, the pharmacokinetic drug profile and sometimes assessment of phamacodynamics can be drawn[5]. In phase II stage, provide clinical data across a dose range and help to assess dose-response relationship[8] and also assess the efficacy/toxicity profile, relative to the comparators [9,10]. In phase III study, provide ultimate safety and efficacy for approval of drug's use in clinical practice, assessment of applicable covariates (patient subpopulation-demographics, co-morbities, concomitant medication and so on) impact, establish or confirm dose exposure-response relationship in target population/subpopulation and dose adjustment in special population. Also validate the population PK/PD model[8]. A PK/PD model not only describe, but also predict distinct situations, such as scaling between preclinical to clinical trials, multiple dosing schemes, or different routes of administration[1].

Recently, there are many novel approaches evolved in modeling and simulation they are population PK/PD analysis, individualized analysis and many PK/PD softwares like Win-Nonlin employed to get accurate results for a dosage form or dose.

Advantages

- It is advantageous in crucial decision making in dug development stage to provide information about safety and efficacy of new compounds fast and at lower cost[2,4].
- Risk assessment of chemical mixtures[11].
- Reduces the necessity of using large uncertainty factors because of its superior.
- Capability of scientifically sound extrapolations between species and doses[6].
- Easy to study toxicity produced by xenobiotics in the body[12,13].
- Best alternative approach to developing personalized medicines.
- Useful to predict the accurate results, minimize the errors and decrease number of study population.

Table 1: Role of PK/PD modeling in different drug development stages [2,4]

Preclinical phase	o	Selection of optimal compound (From pool of compounds)
	o	Prediction of EC_{50} (potency)
	o	Provides basic information to proceed clinical phases
	o	Predict first dose to administer in Phase-I
	o	Prediction of covariates (protein binding, species differences etc) effects on efficacy and activity
	o	Assessing oral bioavailability and hepatic clearance
	o	Assessing drug-drug interactions
Clinical Phase-I	o	Provides data about tolerability, PK and PD.
	o	Reliable even in sparse sampling condition
	o	This information is valuable to design phase-II studies
	o	Even PK is nonlinear this model help for prediction of relevant parameters
	o	Model of multiple dose data can give a chance to identify enzyme auto-induction or the tolerance development.
Clinical Phase-II	o	Assess track of disease progression and dose-response to the medication by drug-disease model
	o	Test dissimilar study designs
	o	Give an idea to design study according to the experimental conditions
	o	Design optimal dosing and sampling outlines.
	o	Assess the effects of covariates
	o	Assess the benefit/risk ratio of dosage or with comparators
	o	Simulation of outcomes
Clinical Phase-III	o	Final confirmation of the efficacy and safety
	o	Gives a direction to use drug in clinical practice
	o	Confirm or institute dose exposure-response relationship in target population
	o	Assess the impact of applicable covariates (patient –demographics, co-morbidities, concomitant medication
	o	Assess the dose adjustment in special population

PK/PD MODELS

Depending up on the concentration at active site and time variant/invariant variables of PK/PD models are categorically classified.

A) Steady state PK/PD models

When the concentrations of the active moiety at the site of action are constant and the PD parameters are time-invariant, the system is said to be kinetically at steady state. This is achieved with long-term intravenous infusions or multiple-dose regimens. Several basic PK/PD models have been used to describe concentration-effect relationship in this situation.

i) Fixed effect model (quantal effect model): It relates a certain drug concentrations with statistical (logistic regression analysis) likelihood of one (or several) effects to be present or absent. For example, the clinical effects of general effects are quantal (response vs. no response) rather than continuous. In this condition, logistic regression analysis has been used to derive concentration vs. response/no response relationship and estimation of the concentration with 50% probability of no response [14]. Since the threshold concentrations will vary among patients, the probability of the effect to be present at a certain concentration will be a function of the threshold concentration in the population [15].This approach may be useful in the clinical setting as an approximation of dose–response relationships but has major limitations for the prediction of complete effect–time profiles.

ii) Linear model: This model overtures observed drug effect is directly proportional to the drug concentration, when the concentration is low in relation to EC_{50}.This model only applies to measured effects with physiological baseline such as blood sugar, blood pressure, etc. It also predicted that linear relationship between central activity and diazepam plasma concentrations [16]. It also shares with the E_{max} model the property of prediction no effect when the drug is absent. The advantageous corner of this model resides in that parameters estimation easily performed by linear regression. However it excludes the prediction of maximum effect. Pharmacodynamically this model is illustrated by equation (1), where S exemplify the effect stimulated by one unit of C and E_0 represents the value of E when no drug is present.

$$E = S.\ C + E_0 \qquad (1)$$

iii) Log linear model: This model was gestated on the observation that when the concentration-effect is hyperbolic, the log-concentration-effects relationship is roughly linear in the range of 20-80% of E_{max}. So this model can be considered as special case of the E_{max} model. Main disadvantage of this model is neither to predict no effect when the drug concentration is zero, nor to predict maximum effect. Nonetheless, this model has been used to successfully predict the pharmacological activities of beta blockers [19] and anti-coagulants [17].

It needs to be kept in mind that the linear and log-linear models are useful only for interpolation, but not extrapolation.Mathematical representation of model (Eq: 2), in which S represents change in response elcited by one unit of log concentration *(log C).*

$$E = S.\ log\ C + E_0 \qquad (2)$$

iv) E_{max} model: This model exposes the effect of drug in relation to the concentration. This model was primitively derived from the classical theory of drug-receptor interaction. This model admits two important properties, to predict maximum effect (E_{max}) of drug at concentrations (C) more than EC_{50} (concentration necessary to produce 50% of E_{max}) and the E_0 is the absence of the effect when no drug is present. This model broadly used to characterize myriad of pharmacological effects [18-21].

$$E = (E_{max}.\ C/EC_{50} + C) + E_0 \qquad (3)$$

v) Sigmoid E_{max} model: This model is a generalization of the E_{max} model. The sigmoid E_{max} model was best fitted the concentration–electroencephalogram (EEG) effect relationship of the intravenous anesthetic ketamine and its two enantiomers [22]. In the equation (Eq:4) where E_{max}, EC_{50} and E_0 are possible maximum effect, concentration necessary to produce 50% of E_{max} and E_0 is the basal value respectively. Symbol γ is the sigmoidicity factor or steepness of the curve, if $\gamma = 1$ hyperbolic curve, $\gamma > 1$ for steeper curve and $\gamma < 1$ for a smoother curve.

$$E = (Emax.\ C^{\gamma}/EC^{\gamma}_{50} + C^{\gamma}) + E_0 \qquad (4)$$

B) Nonsteady-state and Time-Dependent PK/PD models

Beneath nonsteady state conditions, i.e., after single doses as well as when time-independent PD parameters are present, basic PK/PD models are ineffective to explain concentration-effect relationships.

Chronological study of the data point's reveals the presence of hysteresis (clockwise/ counter clock wise sense[23]) loop (Figure 1), i.e., the time course of concentration and effect are out of phase therefore delay between the concentrations in plasma and at the effect site is observed. In counter clockwise curve sense the effect rise slowly, they reach peak later, and are sustained plasma concentrations. Several PD mechanisms have been proposed. If distribution into biophase is rate-limiting, a kinetic biophase compartment can be used to explain the disequilibrium between observed concentrations and effects [24]. An indirect mechanism of action, for example, inhibition or stimulation of the synthesis or degradation of endogenous products, can also become rate-limiting, and results in anticlockwise hysteresis [Fig: 1(b)] [25, 26]. Finally, delayed appearance of active metabolite(s) interacting with the same receptors as the parent compound, at steady state or not, also produces anticlockwise hysteresis [27, 28]. In contrast, a clockwise hysteresis means that effect decreases quicker than plasma concentration [Fig: 1(c)], which reveals a tolerance phenomenon to the drug, either by development of a counter regulatory phenomenon or by desensitization of receptors [29, 30] for instance electroencephalographic effects of alfentanil.
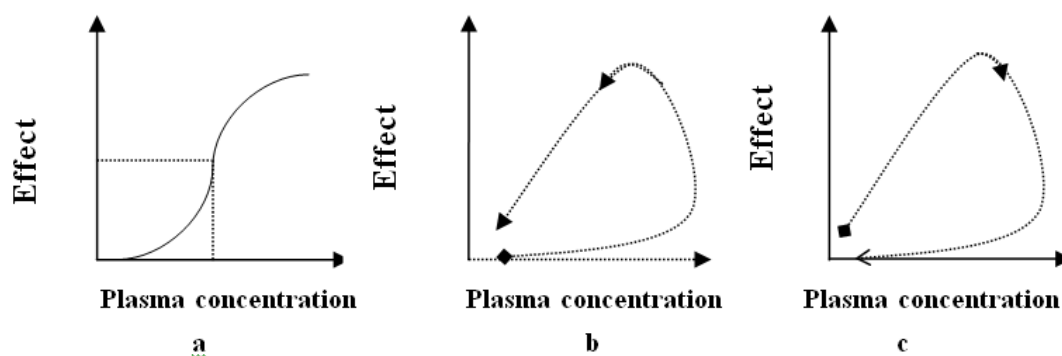

Fig. 1: Schematic representation of effect-concentration data pairs sampled in chronological order (indicated by arrows) a) Sigmoid curve in steady state condition. b and c are non-steady state conditions hysteric loops. b) Counter clockwise loops in the drug effect (E) vs plasma drug concentration. c) Clockwise loop in the drug effect vs plasma concentration

vi) Effect compartmental model: This model is evolved for the drugs which have different PK parameters respective to the organs/tissues. Main advanced concept in indirectly linking PK and PD models was to realize that the time-course of the effect itself can be used to define the rate of drug movement to the effect site as expressed in the effect compartment model proposed by Sheiner [24]. This concept considers a hypothetical effect compartment modeled as an additional compartment of a PK compartment model, and represents the active drug concentration at the effect site. It is linked to the kinetic model by a first-order process with negligible mass of drug in to the effect compartment. Therefore, the rate constant for the transfer between the central and effect compartments is also negligible. Consequently, the time-dependent aspects of the equilibrium between plasma concentration and effect are only characterized by the first-order rate constant (k_{e0}) and explained mathematically (Eq:5) [27].

$$dC_e/dt = k_{e0}. (C_p - C_e) \qquad (5)$$

A semi parametric and non parametric strategy has been developed to estimate of k_{e0} and PD parameters. This approach has been successfully employed to predict the PK/PD relationship of diverse drugs such as nalxone (opiate antagonist), diclofenac (NSAID) and methadone (opioid analgesic) [31-34]. But it is not suitable for a fairly large number of different pharmacological effects, and it does not help to elucidate some underlined mechanisms of pharmacological effects

vii) Physiological indirect response models: Indirect response models (IDR) are models for drugs whose mechanism of action consists of either inhibition or stimulation of physiological process involved in the elaboration of the clinical expression of observed effect. Therefore if the mechanism is at least partially and understood, the PK/PD link may evolve from the abstraction of numbers to a physiological mechanism oriented tool. Considering this point mathematical explanation is done known [23].

The rate of change of the response over time in the absence of drug can be described by a differential equation [Eq. (6)]:

$$dR/dt = k_{in} - k_{out}. R \qquad (6)$$

Where k_{in} represents the zero-order constant for the production of the response and k_{out} the first-order rate constant for loss of response. Depending on whether k_{in} or k_{out} are either inhibited or stimulated by the drug, four different sub models have been developed in which the drug effect is mediated by an E_{max}-like model. These are equations are listed below [Eq (7-10)]:

$$dR/dt = k_{in}. I(t) - k_{out}. R, \text{ for inhibition of } k_{in} \qquad (7)$$

$$dR/dt = k_{in} - k_{out}. I(t). R, \text{ for the inhibition of } k_{out} \qquad (8)$$

$$dR/dt = k_{in}. S(t) - k_{out}. R, \text{ for stimulation of } k_{in} \qquad (9)$$

$$dR/dt = k_{in} - k_{out}. S(t). R, \text{ for stimulation of } k_{out} \qquad (10)$$

These consider that $I(t)$ and $S(t)$ are inhibitory and stimulatory functions, respectively, which can be described in terms of where C is the concentration of the drug, E_{max} the maximum effect, and EC_{50} the concentration that produces half of the maximum effect [Eq 11,12]:

$$I(t) = 1 - [C(t) / IC_{50} + C(t)] \qquad (11)$$

$$S(t) = 1 + [E_{max}. C(t) / EC_{50} + C(t)] \qquad (12)$$

While IC_{50} and EC_{50} being the concentrations eliciting 50% of inhibition or the maximum effect (E_{max}), respectively. These physiologic indirect response models have been employed in a variety of studies regarding biological responses such as muscle relaxation, synthesis and secretion, mediator flux, cell trafficking, enzyme induction, or inactivation, among others [35-37].

Mechanism-based models should be preferred because they not only describe the observations but also offer some insight into the underlying biological processes involved, and hence provide flexibility in extrapolating the models to other clinical situations [38].

Modeling criteria

There are so many multiple interposing factors in modeling; it can be divided in to two blocks: 1) that pertaining to the clinical or experimental design, and 2) the data analysis. Diverse models have been suggested to describe the PK/PD relationship depending upon

the nature of drug administration scheme (single doses, multiple doses, long-term infusions, etc.) and the time dependency of PD parameters. Thus, when the system is kinetically at steady state, i.e., the concentrations of the active moiety at the active site are constant (after long-term infusions or multiple doses), relatively simple models are needed to characterize the PK/PD relationship. Otherwise, after single doses (non steady-state condition) and when time-variant PD parameters are present, more complex models are needed to account for phenomena involved in the PK/PD relationship. But, conventional PK–PD approaches, on the basis of empirical, descriptive models, have limited predictive capabilities and, therefore, a more mechanism-based approach is required.

1. Model building steps

Principles for PK/PD modeling was developed in late 1970s [24, 39]. Experimental design is very precious part in the modeling. The successful modeling can be relies up on the well designed study (dose selection and administration, blood sampling points and PD measurements).

There are so many steps to consider before and while modeling. Among those, these steps are very important (Illustrated in Fig 2). First we have to have idea about the kinetics (behavior in body) and dynamics (mode of action) of a drug prior to designing the study and a hypothetical model.
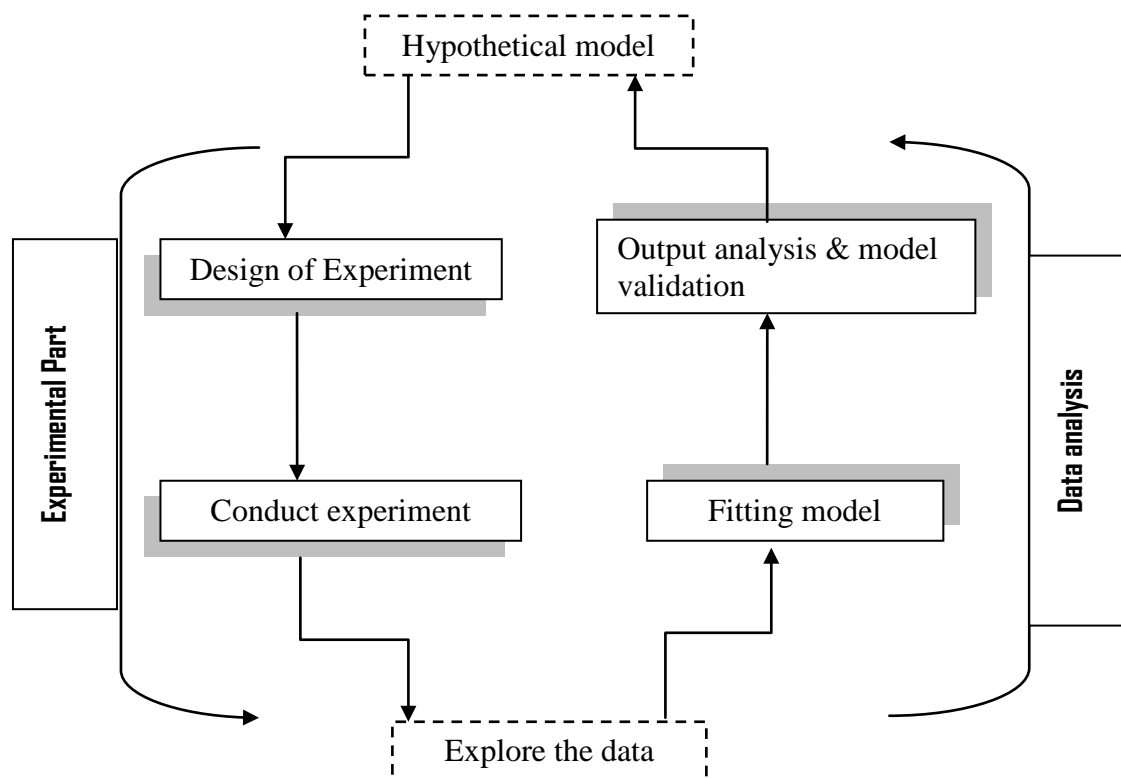

Fig. 2: Hierarchal steps in model building

First Step (I) is assuming a hypothetical model (pre-assumed model) , this is based on the biological process (mechanism of action) of drug induced response and other factors which are further developed or refined, depending on the results. Because pre-assumed model do not have explicitly incorporated quantifiable variables (intra and inter individual variability) and their arbitrary values. Often hypothetical model (the response versus concentration relationship) modeled by E_{max} model [40].

1.1 Designing and performing experiment

As discussed earlier well controlled experimental design is important integral part of the modeling. In the second step (step-II), experimental design, it is a very crucial step in the building process. Now-a-days experimental design is carried out by computer operated statistical software approaches to reduce and avoid bias in the experiment (selection of drug/placebo, target population and treatment allocations) and in the results (false positive results). This experimental design comprises somewhat different to the normal pharmacokinetic studies in which sample collection time points (usually large time points) and pharmacodynamic measurements will be estimated at the same time point which gives accurate relationship and sampling points based up on the duration of action of the drug. For example in anti-inflammatory study blood collection

(for PK parameters estimation) and paw edema volume (for PD measurements) taken at same time point. If the study is properly designed often it can answer to the questions such as 'Does the response reach a maximum or threshold? Are there active metabolites? Is there evidence of the development of tolerance or sensitization to the drug? Especially in case of multiple-dose or repeated dosing or multiple input rate and routes of administration of dosage forms. In step-III actual experiment is performed in specified conditions to gather the data.

1.2 Data analysis

After data gathered, it is necessary that an exploratory (graphic) data analysis to be performed to confirm or suggest modifications to the tentative model(s). The next step is the selection of a model and the fitting of that model to experimental data using regression analysis. This is affected to estimate the model parameters and the precision of parameter estimates. Evaluation of goodness-of-fit, correlation between parameters, residual analysis, parameter accuracy, and challenging with new (or reviewed) data will provide validity to the model [8, 41-43]. This total will move in below step by step.

This stage (step-IV) is very crucial part which is overlooked mostly which give confirmation or suggestion to the assumed model (s). We

analyze the data using various methods and available software programs. Exploratory data analysis (EDA) is performed to evaluate nonlinearities in the data by dose normalizing the plasma concentration curves and plotting dose-concentration-time profiles. Sometimes alternatively plotting plasma concentrations and AUCs (area under the curve) against dose, gender or time to ensure whether the kinetics of a drug are nonlinear over the range studied.

The next important step (step-V) is fitting the experimental data into model which is previously selected by graphical analysis by regression analysis mostly by non-linear regression analysis. By this step we can estimate the model parameters and the precision of the parameters estimates. For this various computer programs are used especially developed WinNonlin (now it is Phoenix Win Nonlin), will derive the initial parameter estimates.

Final step (step-VI) is to evaluate the program output and diagnostics, such as goodness of fit, correlation between parameters, residual analysis, and parameter accuracy and precision. This step explains how the model explains the data and comparisons of competing models. Plots of absolute and weighted residuals (residual plots) versus the independent variable (like time) or the predicted variable (such as concentration) or observed or predicted data superimposed on a linear and semi-logarithmic scale will give total information about the model predicted data. This provides the final answers to assess the suitability of the selected model(s), after this model is validated by testing a new set of experimental data. This validated model either used for the new studies design purpose or to fit a new set of data.

SOFTWARE APPROCHES

The discipline of pharmacokinetics - pharmacodynamic has also been advanced by the general availability of iterative computer methods for nonlinear regression analysis. In the pre-computer era, only the simplest modeling problems could be solved by approximation, usually after data transformation or linearization. Now, complex problems involving simultaneous determination of a number of clinically relevant pharmacokinetic variables can be rapidly solved, including numerical estimates of the statistical strength of the solution. Iterative nonlinear regression procedures expeditiously solve the problems of fitting theoretical models to actual data.

On the other hand, PK/PD models are usually complicated by the need to jointly consider the time-course of drug concentration, nonlinear equations that relate effect to concentration, and the usual requirement of two or three dose levels of drug. Thus, the use of computers for fitting experimental data is essential [44].

There are various softwares available for PK/PD modeling in drug development processes. They are Phoenix WinNonlin, P-PHARM, PH\EDSIM, MEDICI-PK, Modkine, PDx-MC-PEM and JGuiB. These are well user friendly software for not only simple PK/PD models also for population PK/PD models which will support performer. Among these WinNonlin is a very good one, which includes extensive libraries for PK and PK/PD models, and provide tools for table generation, scripting, and data management.

➢ The PK/PD analyses for estimating the PK and PD parameters if each drug as a single agent and the computation of expected tumor growth curves predicted by the TGI add model was carried out using WinNonlin V.3.1 [45].

➢ The PK/PD relationship in development of novel antipsychotic (sertindole and other atypical antipsychotics) was done by WinNonlin v.4 [46].

PK/PD APPLICATIONS IN DIFFERENT THERAPEUTIC AREAS

Some examples of a general characterization of types of PK/PD relationships in different therapeutic areas are summarized below.

Anti-Infective therapy

Antibacterials and Antivirals both face a constant threat of resistance development, which eventually can lead to therapeutic failure [47]. In this area PK/PD indices are intended to normalize the

drug exposure and the susceptibility of the respective pathogens to clinically relevant breaking points [48].For this study mechanism based linkage of PK/PD used. In drug development process of antiinfectives, protein binding and tissue distribution are main PK parameters, minimum inhibitory concentration (MIC) used as major PD parameter to estimate efficacy of compound. Free concentration of antibacterials [42] and antivirals [42] in almost all tissue distribution can be done by microdialylsis technique [49] and MIC of compound can be estimated and PK/PD has been linked to find the effective dose against the pathogens.

Anti-inflammatory therapy

Non-steroidal anti-inflammatory drugs are used to alleviate the inflammation, fever and pain. This group of drugs has effect on the inhibition of the cyclooxygenase (COX) system. Differential specificity towards the iso-form of the enzyme i.e., COX-1 and COX-2 leads to the effective use in the treatments.

Meloxicam, a preferential COX-2 inhibitor, relationship between the plasma concentration and analgesic, anti-pyretic and anti-inflammatory effects in the cat were established by using indirect response pharmacokinetic/pharmacodynamic model. Cats were selected on the basis of possessing similar pharmacokinetic profile with the man. For evaluation of pharmacodynamic properties (efficacy, sensitivity and potency) of the meloxicm, kaolin induced inflammation model used and subcutaneous 0.3mg/kg is the loading dose of the meloxicam to the cat. They used different methods for end point measurements and represented as mean±S.D. IC50 or EC50 values (ng/mL) were found to be 777±124 (body temperature), 841±187 (locomotion variable), 883±215 (pain score), 911±189 (lameness score) and 1298±449 (skin temperature difference). Corresponding mean time±S.D of peak responses (h) were 5.6±1.3, 8.6±3.8, 5.2±5.0, 5.6±3.7 and 4.3±2.34, respectively. From the results it was found that loading dose of meloxicam in the cat similar or somewhat greater than the clinically recommended doses both in the cat (0.3mg/Kg) and humans (7.5-15mg/Kg) [50].

Lumiracoxib, a novel selective COX-2 inhibitor, used as anti-inflammatory drug in the rheumatoid arthritis and osteoarthritis. But failure of the other COX-2 inhibitors in avoiding the cardiotoxicity as well as hepatic toxic it's usage is limited. Here pk/pd model is used to elucidate the therapeutic dose of the lumiracoxib to avoid such toxicological events. For this purpose carrageenin induced hind paw hyperlagesia model in the rat was chosen. Female fasted Wistar rats were injected with saline or carrageenin in the right hind paw, followed by eighter lumiracoxib 0, 1, 3, 10 or 30 mg/Kg of oral lumiracoxib at the time of carrageenin injection or at the 4th hr of carrageenin injection. Antihyperalgesic responses were measured as latency time (LT) to a thermal stimulus. Lumiracoxib pharmacokinetics was described by a two-compartment model. A first-order model, including lag time and decreased relative bioavailability as a function of the dose, described the absorption process.The response model was: $LT = LT_0/(1 + MED)$. LT_0 is the baseline response, and MED represents the level of inflammatory mediators. The time course of MED was assumed to be equivalent to the predicted $fire$ of COX -2 activity and was modeled according to an indirect response model with a time variant synthesis rate. Drug effects were described as a reversible inhibition of the COX-2 activity. The in vivo estimate of the dissociation equilibrium constant of the COX-2 –lumiracoxib complex was 0.24 mg·mL-1. From this study they concluded that this developed model appropriately described the time course of pharmacological responses to lumiracoxib, in terms of its mechanism of action and pharmacokinetics [51].

Antipsychotic therapy

Antipsychotic are the agents which act centrally. Firstly, clinical effectiveness of a compound can be known by selective suppression of the conditioned avoidance response (CAR) which has a high predictive validity for the antipsychotic efficacy. In this the PK/PD predictions of therapeutic effective study–state plasma levels by means of CAR behavior and in vivo striatal dopamine D2 receptor binding in rodents correlates with clinicallly relevant plasma exposure/D2 receptor occupancy levels of the classical antipsychotic

drugs (haloperidol & sertindole, clozapine, riserpidone and Olanzapine).

C.K. Olsen et, al reported that good correlation between the rat dopamine D2 receptor occupancy levels providing 50% response in the CAR test and the dopamine receptor occupancy levels in schizophrenic patients treated with antipsychotics. Thus the combined PK/PD modeling of CAR and dopamine (D2) receptor occupancy data from rats is suggested to be good guidance for the therapeutically relevant dopamine D2 receptor occupancy needed for the clinical effect of novel antipsychotics with dopamine receptor D2 antagonistic properties. This study highlighted the need of PK/PD modeling to the steady state conditions to correctly interpret the correlation between dose, plasma levels and pharmacological response [46, 52].

Opioid therapy

The effect of opioids usually parallel with the plasma concentrations but with temporal shift. This temporal shift is less in case of alfentanyl or sufentanyl and very long with the metabolites of morphine, morphine-6-glucuronide (M6G). This delay between the plasma concentration and effects is accounted by the introduction of a hypothetical effect compartment, which is linked to the plasma compartment by a first-order transfer function with a rate constant k_{e0}. Then the effects are linked to the concentrations at the effect site by standard pharmcodynamic models or powerful models [53]. Since the PK/PD of opoids has been repeatedly assessed, using EEG parameters, pupil size and experimental and clinical pain as affect measures. Then the PK/PD modeling is come in to the existence to explain the time course of the clinical effects of opioids after various dosing regimens and also used for target infusion regimens by means of computerized infusions [54]. In this, indirect link of PK/PD model was simulate to quantify the relationship between infusion duration and the time required for the recovery after termination of infusions. From this model Jorn Lostch concluded alfentanil is preferable drug for infusions in case of the quick recovery patient is desired among the fentanyl and morphine [55].

Cancer chemotherapy

Anticancer treatment with the paclitaxel and etoposide results not only in benefecial therapeutic effects also in adverse conditions like leucopenia and neutropenia. To describe such condition a physiological indirect response model was established. This model was successfully relates the drug concentrations vs. time curve to the time course of leucopenia. This model consisted of two compartments corresponding to leukocyte pools in bone marrow and peripheral blood, because anticancer drugs work on myeloid cells in bone marrow, whereas leukocyte counts are measured in peripheral blood. PK model parameters (concentration- time curve) of anticancer drugs were used to input to the model. The model consisted of two compartments corresponding to leukocyte pools in bone marrow and peripheral blood, because anticancer drugs work on myeloid cells in bone marrow, whereas leukocyte counts are measured in peripheral blood. A concentration–time curve (in terms of PK model parameters) of an anticancer drug was used as input to the model. It was assumed that only mitotic components consisting of myeloblasts to myelocytes are sensitive to chemotherapeutic agents. It was hypothesized that the inhibition of leukocyte production in bone marrow was controlled by the exposure of myeloid cells to anticancer drugs when they are in the sensitive cell stages. The following parameters were estimated: lag-time, 58 ± 38 (mean ± SD) hours before the leukocyte count started to decline; exposure giving 50% inhibition of leukocyte production (IC), 12.1 ± 6.1 μg · h/mL; and sensitive period, 288 ± 64 hours. These estimations were within physiologic ranges. In validation, leukopenia after 24-hour infusion of paclitaxel or 14-day infusion of etoposide was also explained by the model. Age was significantly negatively correlated with IC of paclitaxel (P = .039).With the model mechanistically developed, the entire time course of leucopenia or neutropenia after chemotherapy with anticancer drugs could be successfully described, and it may provide a platform for physiological analysis of PD of anticancer drugs [56].

POPULATION PK/PD MODELLING

Population modeling term implies that modeling studies undergone in the different type of populations such as different species, age, polymorphic phenotypes, disease state and ethnic variations. This method is far better than individual PK/PD studies which concludes a wide variable effects on the outcome of the parameters such as *Emax* (maximum response) and *EC₅₀* (concentration producing one half of the maximal effect) among the populations. Within a same species, the intra-individual and inter-individual variability in PD parameters is likely to be as high as or higher than that associated with the PK parameter estimates. However, the primary source of between-species variability is often attributable to variability that is mainly of PK origin. For example, it appears that the (free) drug plasma concentration required to elicit a given response is rather similar between species, whereas the corresponding dose for eliciting the same effect can differ widely. To date there are many software packages like NONMEM ® that provide nonlinear mixed effects modeling [57].

The supreme goal of the population PK/PD analysis is to provide the information that can be used to establish guidelines for the individualization of dug dosage regimen and dose setting in the target population.

For instance, Mould et al. characterized Aletuzumab (a monoclonal antibody) pharmacokinetics and its exposure-response relationship with white blood cells (WBC) count in 67 patients with B-cell chronic lymphatic leukemia (CLL), by selecting nonlinear mixed effect model. Logistic regression was used to relate the measures of drug exposure to tumor response in the individuals. Alemtuzumab pharmacokinetics were best characterized by a two-compartment model with nonlinear elimination where V_{max} (μg h⁻¹) was [1020 × (WBC count/10 × 10⁹ l⁻¹)⁰·¹⁹⁴], K_m was 338 μg l⁻¹, V_1 was 11.3 l, Q was 1.05 l h⁻¹ and V_2 was 41.5 l. Intersubject variability (ISV) in V_{max}, K_m, V_1 and V_2 was 32%, 145%, 84% and 179%, respectively. The reduction in WBC over time was modelled by a stimulatory loss indirect response model with values of 18.2 for E_{max}, 306 μg l⁻¹ for EC₅₀, 1.56 × 10⁹ cells l⁻¹ h⁻¹ for K_{in} and 0.029 per h for K_{out}. The probability of achieving a complete or partial response was ≥50% when the maximal trough concentration exceeded 13.2 μg ml⁻¹ or when AUC₀₋τ exceeded 484 μg h⁻¹ ml⁻¹. From this approach they concluded that alemtuzumab displayed variability in both in pharmacokinetics and pharmacodynamics, difference in time- and concentration-dependent pharmacokinetics with large inter-individual (patient) variability, which was probably reflective of differences in tumour burden among patients. A direct relationship between maximal trough concentrations and clinical outcomes was observed, greater probability of positive tumour response was resulted by increasing alemtuzumab exposure [58].

Another good example in this working area, that Albert Dahan et.,al performed a study on the effect of S(+)-keatmine on pain scores in Complex Region Pain Syndrome type-I (CRPS-I) by population PK/PD model approach to enhance the effectiveness of the pharmacological treatment in the target population. The results disclosed that S(+)-keatmine and its metabolite showed significant effect on the patients(n=60). The chance for ananalgesic effect from ketamine and placebo treatment was 67±10% and 23±9% (population value ± SE), respectively. The pain data were well described by the PK–PD model with parameters C50 =10.5 ± 4.8ng/ml (95%ci4.37–21.2ng/ml) and t½ for onset/off-set=10.9±4.0 days (5.3–20.5 days) in relieving pain and the obtained data suggested the events triggered (desensitization of excitatory receptors system) in brain by keatmine was slowly abated when the ketamine molecules were absent [59].

CONCLUSION

This review explicitly answered the question like what is PK/PD modeling, how to build a model, what are the steps to be followed in model building process, what are the different models for different situation and applications of modeling criteria in different field of study. Apart from these, from the above critical study we can conclude that PK/PD is an invaluable tool in all of the drug development phases i.e., form the preclinical to the late drug

development stages without having any doubt in the data collected. It is useful in the development of lead compounds, dose selection in safety and efficacy corner. After setting a dose to a dose form, population PK/PD models are used to estimate the variability in the target population to assess the sufficient dose and dosage form for them. These varying results may be impact of covariates like demographical, pathological and physiological variations. By using population approach we can minimize the risk factor of the dose and also this technique has given strength to the one dose not for all.

From the above exemplified data we can say that modeling is essential not only research field but also in the academic study programs where we can predict such variability in the initial preclinical stage and we can explore these valid results in to clinical phases to reduce time for a drug development.

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