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Pharmacometrics: Concepts and Applications to Drug Development

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ABSTRACT:
Drug development process continues to be very expensive and time consuming. Approximately it costs 0.8 to 1.4 billion dollars and 10 to 15 years for transforming an idea toa marketable drug. Effective tools are need of an hour which aids in faster and efficient drug development. Pharmacometrics is the science of quantitative pharmacology which characterizes and measures the dose response relationships by using statistical and mathematical methods. By generating the knowledge from preclinical to phase IV studies, it provides knowledge driven decision making in the drug development process. Some of therapeutic applications includes molecular screening, biomarker identification, efficient trial design and also useful in dosage individualization in clinical settings. This subject review will brings about views on background of pharmacometrics and its concepts and also provides information on various PK/PD models, population analysis and some case studies to show the impact of pharmacometrics on drug development. The pharmacokinetic and pharmacodynamics model and simulation tools incorporation into the field of drug development not only improves the drug development process but also reduces the cost from clinical trial failures and withdrawal of drug from the market.
Key words :pharmacometric ,pharmacokinetics , pharmacodynamic ,central tendency

I. INTRODUCTION

Scientific revolutions in biomedical science achieved better prevention, treatment, and cure of serious illnesses and raised new hopes for continuous progress. However, there is growing concern over an issue that so called new basic science discoveries made in recent years may not quickly yield more effective, more affordable and safer medical products for patients[1]. This is because the current drug discovery process is becoming increasingly challenging, inefficient, and costly. During the last several years, the number of new drugs and biologic applications submitted to FDA has declined significantly and the number of innovative medical device applications has also decreased. It usually takes 10-15 years and costs nearly 1.4 billion dollars to transform and idea in to drug. Millions of molecules are screened but only 1-2 drugs finally come to market. So to meet the demand development toolkit containing powerful new methods such as animal or computer based predictive models, biomarkers for safety and effectiveness, and new clinical evaluation techniques is urgently needed[2]. There is also a development in trends like drug utilization review, generic competition and therapeutic substitution, which increases pressure for the drug development industry to deliver high value therapeutic agents. FDA has highlighted the importance of model based drug development.

PHARMACOMETRICS DEFINED

Pharmacometrics is the science of developing and applying mathematical and statistical methods to characterize, understand, and predict a drug's pharmacokinetic, pharmacodynamics and biomarker outcomes. It involves and integrates several research disciplines like pharmacokinetics (PK), pharmacodynamics (PD), pathophysiology and statisticsPharmacometrics was primarily based on modelling and simulation of data, which includes population pharmacokinetic (PPK) analysis, exposure-response determination for drug efficacy and safety, clinical trial simulations and disease progression modelling. Through pharmacometrics one can quantify the uncertainty of information about model behaviour and rationalize knowledge driven decision making in the drug development process.

APPLICATIONS

Pharmacometrics can be applied at all stages of the drug development, from the pre-clinical phase through various phases of clinical

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trials. Potential applications range from molecule screening and identification of biomarkers and surrogates, dosing regimen and trial design selection, prognostic factor and benefit/risk evaluation. By applying these methods we can get all prior and current information, to maximize knowledge and efficacy of drug development programs.

CLINICAL TRIAL DESIGN

Most of the time clinical trials fail to demonstrate effectiveness or safety, often due to ignorance of prior knowledge, both drugs specific and nonspecific and lack of efficient dosing strategies[1]. Disease drug trial models and clinical trial simulations are very useful tools that can help reduce such trial failures. Potential benefits include comparison of various study designs, dose and safety outcomes, sample size and power determination, and evaluation of drug interactions and co-morbidities. The resources needed to perform the pharmacometric analyses are very less compared with the costs of unsuccessful trials. For instance, nesiritide, a sterile, purified preparation of human B-type natriuretic peptide developed for the treatment of acute congestive heart failure, was initially not approved because the dosing regimen used in the first registration trial was sub optimal. Modeling led to suggestion of a new, optimal dosing regimen, and results of simulated trials based on this regimen matched well with those of the second registration trial that led to eventual approval of the drug[3].

DOSE OPTIMIZATION

Exploring different dosing strategies in clinical trials is often impractical, costly, and in some cases, unethical. By doing simulations we can explore all competing dosing schemes and finally can select an optimal strategy. If there is no single dosing scheme is available to achieve target drug exposures in majority of patients, there may be need for dose individualization and therapeutic drug monitoring (TDM). Modeling and simulation can help forecast this need and provide a TDM strategy[1].The ability of developed exposure response relationship to support approval of a dosing regimen not directly studied in clinical trials is in fact one of the strongest merits of modeling and simulation. Unfortunately, this tool is not being fully exploited currently.

COVARIATE / PROGNOSTIC FACTOR DETERMINATION

Apart from dose ranging studies, the characterization of a new drug involves many studies to identify influential covariates such as body size, age, gender, food intake, co-morbidities, co-medications, and others. While effectiveness and safety data may not be collected in all the studies it can simulated from a previously developed drug model[4]. For ex.Sugar was a once a day controlled release formulation of the drug Nisoldipine, which was approved in the U.Sfor the treatment of hypertension. Food was found to increase the bioavailability (Cmax increases up to 245%). The influence of these higher drug concentrations on lowering of blood pressure was evaluated using simulation of the drug effect under fed condition from a previously developed exposure response model. Even though the Sular label recommends administration on an empty stomach for optimal bioavailability, these simulations results alleviates the worry for safety concern of a large drop in blood pressure. Hence, there is no safety warning in the label for the drug to not be administered in a fed condition.

SPECIAL POPULATIONS

Pharmacometric analyses helps to understand the unique features of clinical pharmacology of special populations such as paediatrics, geriatrics, renal or hepatic impairment etc.For anti-cancer drug docetaxel, the exposure-response relationship in patients with cancer was establishedin identifying that patient with liver impairment, to be more prone to grade 4 neutropenia[5]. This important finding improved the safety profile of the drug and results in dosing recommendation for patients with hepatic insufficiency in the label. A well-defined exposure response relationship of a drug in adults for a biomarker, surrogate or clinical endpoint, can facilitate development of the same drug for use in paediatrics. Modeling and simulation is a powerful tool that can be used to provide good trial design, rational dosing recommendations and useful labelling information in paediatrics.

DISEASE MODELS

A disease model is a mathematical representation of a given biological system in the absence of drug that attempts to quantify the time course of the disease[6]. The important models that capture the relevant aspects of disease are the relationship between biomarkers and clinical outcomes and the natural disease progression.

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BIOMARKERS AND CLINICAL OUTCOMES

In several cases, particularly when clinical endpoints occur after prolonged periods of time, biomarkers are used as outcomes in clinical trials rather using the actual clinical endpoints. Establishing the relationship between biomarkers and clinical outcomes for both efficacy and safety for a particular disease conditionis important aspect of disease modeling, and can help develop surrogate endpoints. These models help in trial design optimization and risk projection based on biomarker data. Systems biology models are based on an understanding of the underlying biological system, much like physiologically based models[7]. Semi mechanistic models sufficiently simplify the biological system to be able to describe the available data well[8]. For instance, in the case of diabetes, a detailed systems biology model with more than 50 parameters as well as a semi mechanistic model has been proposed[9]. While the systems biology model takes into account glucose and HbA1c data, as well as other related information such as blood pressure, cardiac output, family history, cholesterol, and smoking status. The semi-mechanistic model focuses on just the glucose and HbA1c information. Similarly, the outputs of the systems biology model include risks of retinopathy, nephropathy, and neuropathy, while the semi-mechanistic model is restricted to prediction of changes in glucose and HbA1c.

NATURAL DISEASE PROGRESSION

The natural disease progression aspect of disease modeling aims at describing the time course of changes observed in the clinical outcome. For example the natural progression of Alzheimer's disease as measured by the Alzheimer's disease Assessment Scale Cognitive score has been described using empirical models[10]. Even mechanistic models, which are more generalizable, can also be studied.

POPULATION ANALYSIS

A population model typically comprise of structural and statistical model components. Structural models are deterministic in nature, and account for population or 'fixed effects' but do not account for variability. Examples are the typical value of systemic clearance (CL) for a 70 kg individual and the mean potency (EC50) of a drug.Statistical models are stochastic in nature, and account for the variability or 'random effects' seen at both, the individual and the observational levels. A population model would include three statistical models: between-subject variability (BSV) model, between-occasion variability (BOV) model, and within-subject variability (WSV) model BSV signifies deviations among different subjects and BOV signifies deviations among different occasions. WSV signifies deviation between predicted and observed values for each subject, and may be the result of measurement error or even model misspecification. Nonlinear mixed effects models are called so because they attempt to account for both, fixed and random effects together. The "mixed effects" concept is depicted in Figure 1.Consider a one-compartment PK model where the drug is given as an intravenous bolus and the volume of distribution (V) is identical in every individual.

then concentration in the 'ith' subject at the 'jth' time point (Cij) can be described using the following equations:

Equation 1

$$\hat{Cp}_{ij} = \frac{Dose_i}{V_i} \cdot e^{-\frac{CL_i}{V_i} t_{ij}}$$

Equation 2

$$CL_i = CL_{pop} + \eta_{CL,i}$$

CLi is the estimated clearance of the 'ith' subject, CLPOP is the estimated population mean clearance, η CL,i is the difference between the population mean and individual clearances and εij is the residual error of the 'jth' sample of the 'ith' subject.

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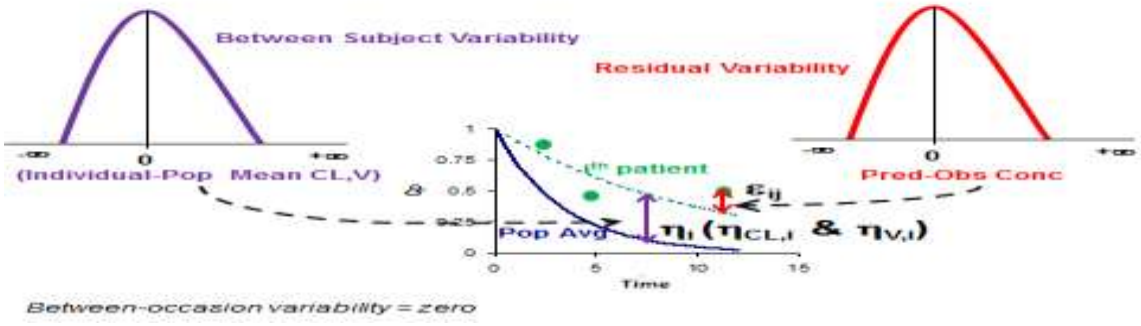
Figure 1: Conceptual framework for nonlinear mixed effects modeling



ANALYSIS METHODS

Population analysis estimates the mean value of relevant parameters (such as CL, V and EC50) in the population of interest, the variances in these parameters as well as residual variability of observations. It also explains the observed BSV using patient covariates such as body size, age, genotype etc. The known methods for performing a population analysis are: naïve pooled, naive averaged, two-stage (TS), and nonlinear mixed effects (NM) or one-stage analysis.

In naive pooled analysis, individual observations from all subjects are pooled to obtain average PK parameters. A minor variation of this method is the naïve averaged analysis which involves determination of the mean of the data at each time point. Both these methods provide only the central tendency of the model parameters and no random effects are estimated. These methods are used more often for preclinical data and are appealing because of their simplicity. However, since between-subject variability is not estimated and cannot be accounted for using covariates, the potential applications of naïve pooled or naïve averaged analyses are very limited.

In two-stage analysis, the first stage involves estimation of the average parameters for each subject from their individual observations, while the second stage involves the estimation of the population mean and variance of the parameters. Estimates of both, the central tendency and the inter-individual variability can be obtained reasonably well. The Two stage method requires collection of rich data to have sufficient samples per subject, which is the requirement with experimental data. One concern is this method assumes that the individual parameters, estimated in stage one, are known without any uncertainty. More serious drawbacks include the inability of themodel sparse data and concentration (or dose) dependent nonlinear processes. The conventional PK non-compartmental analysis (NCA) is a type of two-stage population analysis approach.

In non-linear mixed effects analysis, data from all subjects are simultaneously modelled to yield estimates of both, population mean parameters as well as variance. Since both stages of the TS method are performed in one step, the NM technique is also known as the one-stage method. Nonlinear mixed effects modelling is perhaps the most powerful technique for analyzing both rich and sparse data. One of the main advantages of the NM method is its ability to conduct metaanalyses which enables incorporating all data across a drug development program. The primary disadvantage of this method is that advanced software are required for the analysis, which makes compulsory for special training for its use, while learning resources are limited. In addition, these analyses can be highly timeconsuming.

EVOLUTION OF PK/PD

Parallel to the evolution of pharmacokinetics first attempt have been made to account for the dynamic nature of pharmacologic responses. For numerous directly and reversible acting drugs, the intensity and time course of effect could be related to the time course of the plasma concentrations measured. Based on these relationships and known pharmacokinetic parameters, predictions on the intensity and decay of pharmacologic effects were possible. Establishing the dose-concentration effect relationships remained in most case limited to drugs with a straight correlation between observed effect and measured concentration and failed if the intensity of effect lagged behind the concentrations. The temporal dissociation between effect and concentration that causes a counter clockwise hysteresis in the effect versus concentration

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relationship could be overcome by the effect-compartment approach .This concept facilitated to link pharmacokinetics and pharmacodynamics for a wide range of therapeutic compounds.

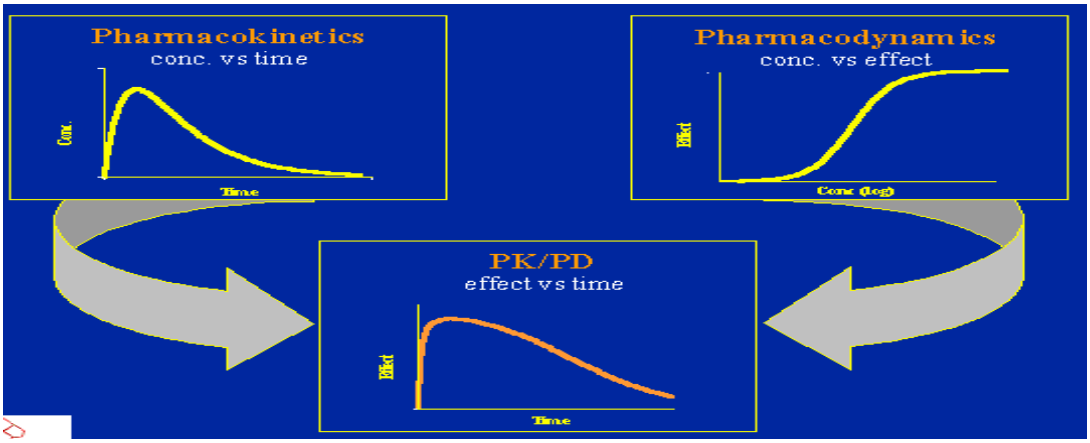

Fig 2: PK/PD modelling combination of classical pharmacology disciplines pharmacokinetics and pharmacodynamics

CLASSIFICATION OF PK/PD-MODELS[11]

Integrated PK/PD-models can be classified according to the manner in which the measured pharmacokinetic and pharmacodynamics data are related to each other. Four different models have been proposed that might be used to distinguish between different basic modelling concepts. These characterize the link between the concentration and the response mechanism accountable for the observed effect, the response mechanism by which the effect is mediated, The different types of PK/PD models

- Direct link versus indirect link models.
- Direct response versus indirect response models.
- Soft link versus hard link models.
- Time-variant versus time-invariant models.

DIRECT LINK VERSUS INDIRECT LINK MODELS

The effect is provided by the concentration at the effect site. The relationship between the drug concentration in plasma and at the effect site may either be constant or undergo time dependent changes.Under pharmacokinetic steady-state conditions, plasma and effect site concentration are in equilibrium, and thus their ratio is constant. Under non steady-state conditions, however, re-equilibration between the two concentrations may be slow due to the distribution process involved. As a consequence of such a distributional lag, the ratio between plasma and effect site concentration would change with time resulting in a temporal dissociation between the time courses of measured concentration and observed effect. For example, concentration maxima would occur before effect maxima, effect intensity might increase despite decreasing plasma concentrations and would persist beyond the time drug concentrations in plasma are no longer determinable. A counter-clockwise hysteresis loop would be the consequence in an effect vs. concentration plot.

These general differences in the link between plasma and effect site concentration can be used to classify PK/PD-models in either direct or indirect link models.

DIRECT LINK MODEL

For direct link models, the measured concentration in plasma is directly linked to the effect site concentration. The equilibrium between both concentrations is assumed to be rapidly achieved and thus their ratio is constant, under pharmacokinetic steady-state as well as non-steady-state conditions.so the measured concentrations can directly serve as input function in the pharmacodynamics model component, thereby directly linking measured concentration to the observed effect

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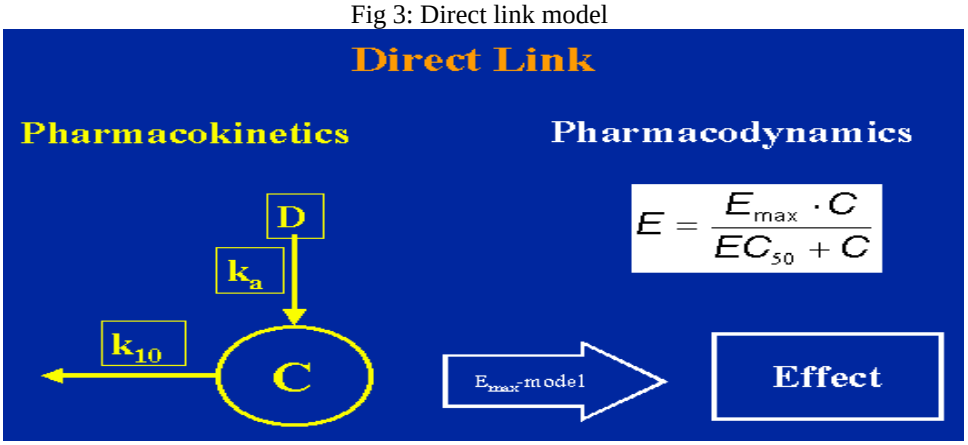
Fig 3: Direct link model



In that case, concentration and effect maxima would occur at the same time and effect vs. concentration plots would lack any hysteresis if the response is directly mediated.An example for a direct link model was provided by Racine-Poon et al[12]. who directly related the serum concentration of the anti-human immunglobulin E (IgE) antibody CGP 51901 for the treatment of seasonal allergic rhinitis to the reduction of free IgE via an inhibitory sigmoid Emax-model

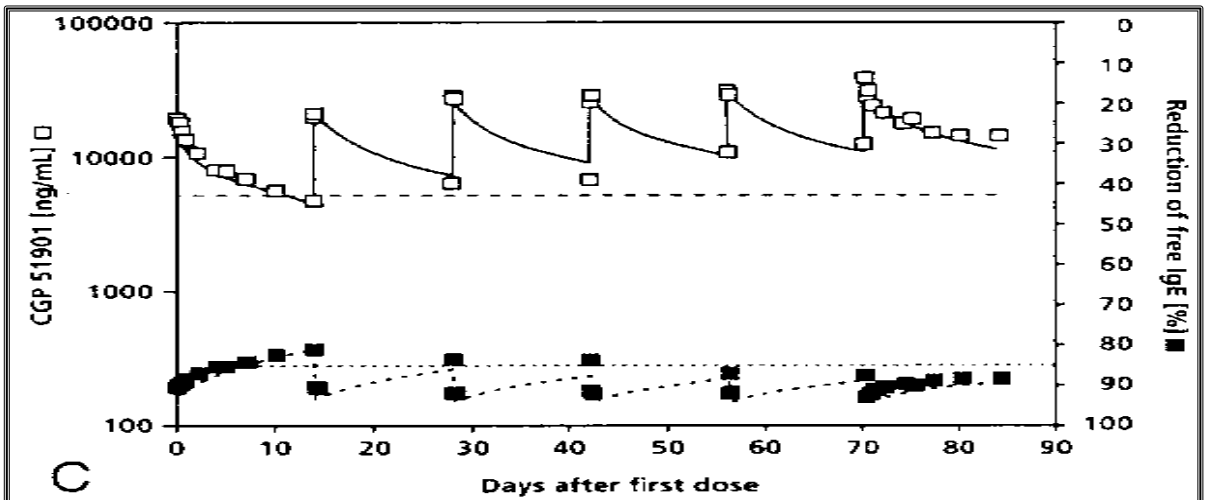


Fig 4: Observed (□) and predicted (‾‾) serum concentration of the anti-human IgE antibody CGP 51901

Observed (□) and predicted (‾ ‾ ‾) reduction of free IgE in one representative patient, given six doses of 60 mg biweekly.

The predictions are modeled with a directly linked E_{max}-model

INDIRECT LINK MODEL

In contrast to that, indirect link models are required if there is a temporal dissociation between the time courses of concentration and effect, and the observed hysteresis in the concentration-effect relationship is most likely caused by a distributional delay between the concentrations in plasma and at the effect site.In some cases, it could be shown that the drug distribution to the site of pharmacologic activity might be similar to the distribution of the drug into one peripheral compartment of a pharmacokinetic multi-compartment model. Thus, the modelled peripheral compartment concentration profile may serve as input function for the pharmacodynamic model component

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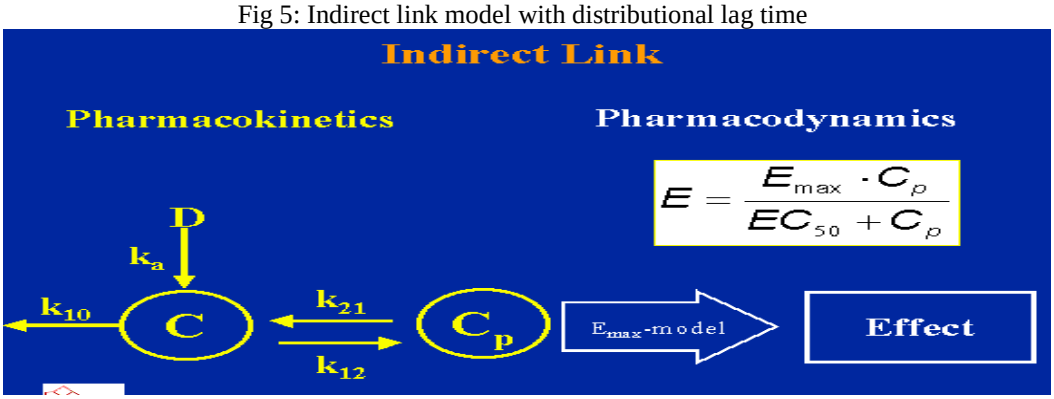
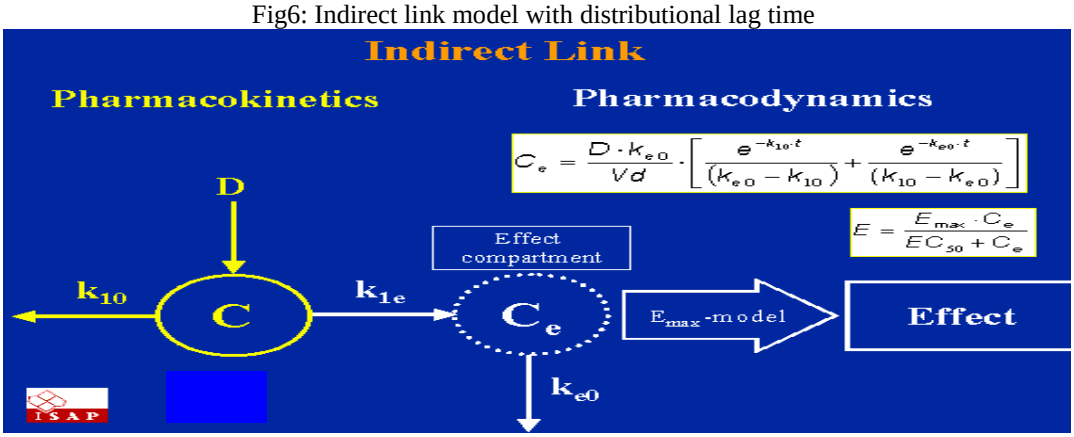
Fig 5: Indirect link model with distributional lag time



A more general approach for an indirect link between concentration and effect was the conceptual advance of the effect-compartment model makes the time course of the effect itself can be used to define the changes in concentration at the effect site and there by leading to a collapse of the hysteresis loop in them concentration-effect relationship. This is accomplished by a hypothetical effect-compartment attached to a pharmacokinetic compartment model that does not account for mass balance and only describes the concentration-time course at the effect site

Fig6: Indirect link model with distributional lag time



The effect compartment can either be linked to a pharmacokinetic one-compartment model or to the central compartment of a multi-compartment model. The link to a peripheral pharmacokinetic compartment whose concentrations are modeled and thus are also hypothetical, however, seems only appropriate, if additional information on the concentration profile in the peripheral compartment is available, e.g. in shape of tissue level measurements Examples for the application of the effect-compartment approach were given by Dingemanse et al. for the EEG effects of the short-actingbenzodiazepine Ro 48-6791

Fig 7:Muscle relaxant effect of d-tubocurarine (DTC)Infusion: 16.8 µg/kg/min for 10 min & 1.2 µg/kg/min for 150 min.

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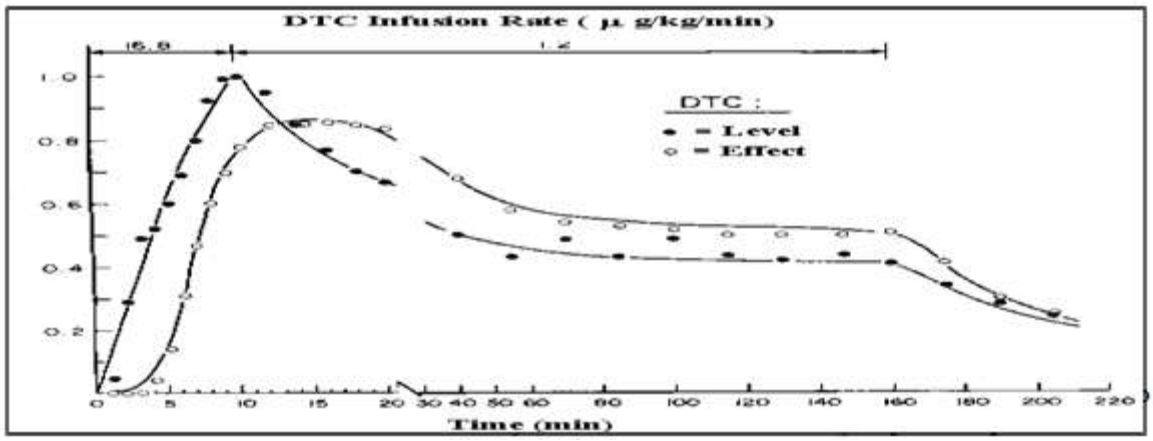
Effect or Fraction of Peak Plasma Level



DIRECT RESPONSE VERSUS INDIRECT RESPONSE MODELS

Dependent on the mechanisms involved, the expression of the observed effect might either be directly related to the concentration at the effect site or secondary to one or several intermediary response steps.

DIRECT RESPONSE MODEL

For direct response models the observed effect was found by the effect site concentration without time lag. Thus, the involved transduction and response mechanisms mediate the effect rapidly enough to directly account for each change in effect site concentration without delay. The previously presented examples for direct link models also represent direct response models. For indirect link models, time courses of plasma concentration and effect are dissociated, but this temporal delay is caused by distribution process whereas the effect site concentration is directly transformed into the observed effect. Hence, the presented examples for effect compartment models as well as those models using peripheral pharmacokinetic compartments as effect site concentrations can also be classified as direct response models

Apart from distributional process, temporal dissociation between the time courses of concentration and effect might also be caused by an indirect response mechanism resulting again in a counter clockwise hysteresis for the concentration-effect relationship. The elaboration of the observed response, for example, may be secondary to a previous, time consuming synthesis or degradation of an endogenous substance. If the temporal dissociation between concentration and effect cannot be attributed to distributional process, mechanism-based indirect response models should be applied.The response itself can be modulated through the effect site concentration by either stimulating or inhibiting k^0_{in} (Fig.8) or k_{out} (Fig.9) via an Emax-model.Indirect response modeling has been applied for numerous drugs, especially in cases where endogenous substances are involved in the expression of the observed response

Fig 8: indirect response model with formation process

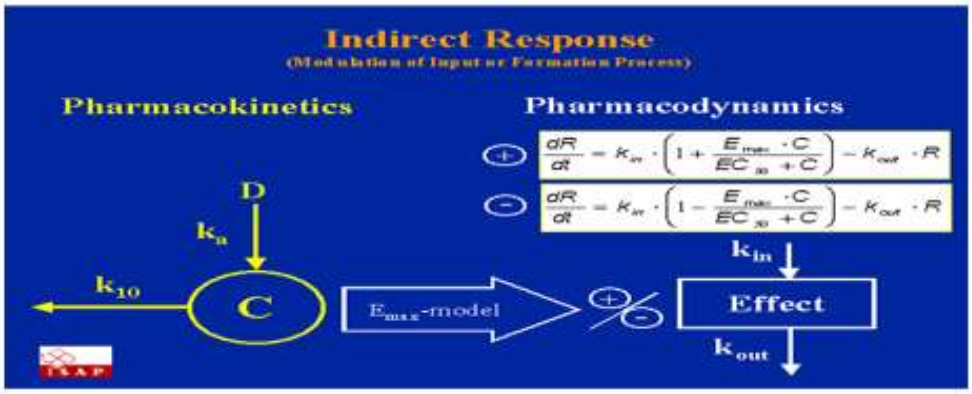


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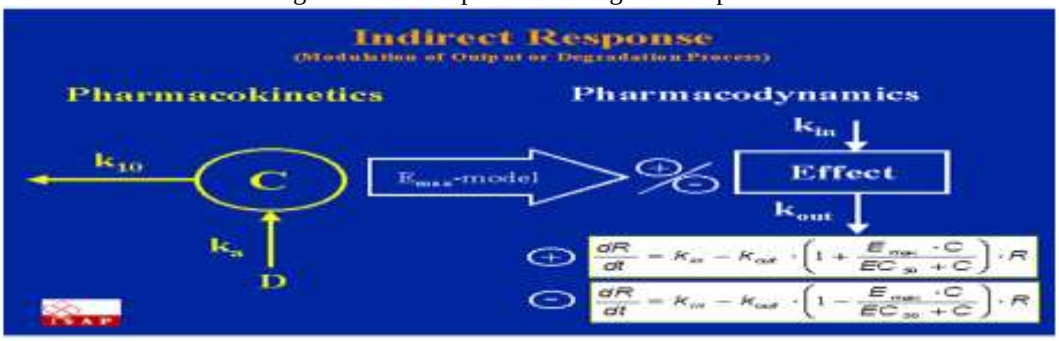
Fig 9: Indirect response with degradation process



HARD LINK VERSUS SOFT LINK MODELS

PK/PD-models may also differ in the way they are established and use the provided information, clinical measurements of concentration and effect as well as additional experimental data regarding the underlying mechanism of action.

SOFT LINK MODEL

Soft link models typically utilize measured data setsconcentration and effect, to define the link function between pharmacokinetics and pharmacodynamics. Thus, the flow of used information is bidirectional (Fig.10) and the link, e.g., an effect compartment accounts for the misfit between the measured data sets. Hence, effect compartment models typically represent soft link models if they are merely descriptively used to account the concentration effect relationship without further consideration of the involved mechanisms, e.g., dispositional or other, more complex processes. Although the soft link approach has predictive capacity and may be extrapolated to other situations if thoroughly validated, the model development process has clearly a descriptive character requiring concentration as well as effect data.

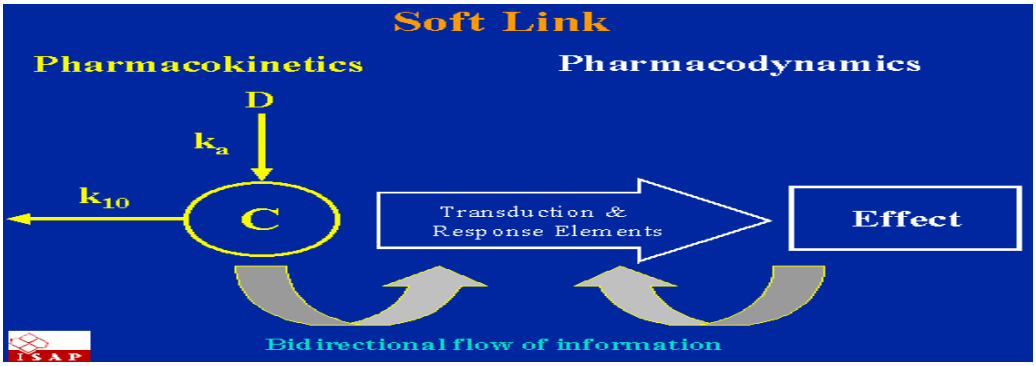


Fig 10: soft link model

HARD LINK MODEL

contrast to the soft link approach, hard link models use a unidirectional flow of information, where the pharmacokinetic data and additional information regarding the mechanisms involved are already used during model development to predict the time course of the effect (Fig.11). Utilized additional information comprises in vitro data like receptor binding affinities and minimum inhibitory concentrations of antibiotics or other mechanism specific variables. Thus, hard link models are mechanism-based models that have clearly a predictive character and allow forecasts of the pharmacodynamic activity of new compounds The hard link approach has been successfully applied in PK/PD-models for different effects of corticosteroids, where it could be shown that the EC50 based on free steroid concentration is comparable to IC50-values obtained from in vitro receptor binding studies. Since all corticosteroids elicit their effect via the same receptors, it was possible to estimate the clinical potency of these drugs based on in vitro receptor binding studies without any experimental clinical work.

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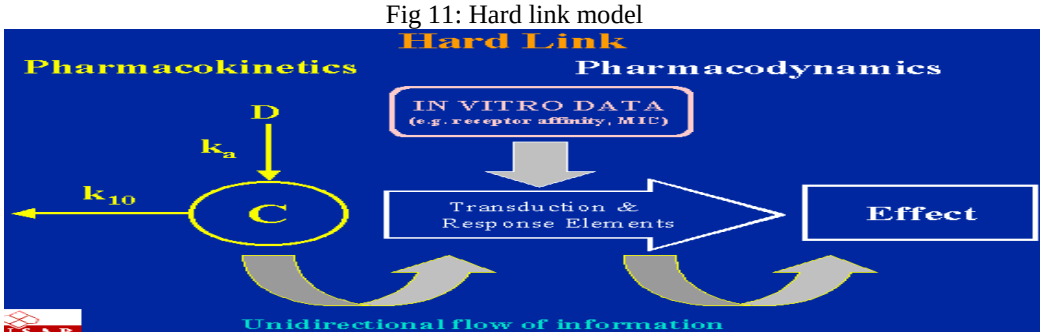
Fig 11: Hard link model



TIME VARIANT VERSUS TIME INVARIANT MODELS

In addition to the presented attributes, PK/PD-models can also be distinguished with regard to the time dependency of their PD-parameters.

TIME-INVARIANT MODEL

For time invariant PK/PD-models, the effect intensity is always secondary to the concentration and the involved pharmacodynamic model parameter stay constant over time. Most drugs follow this rule, with changes in effect solely related to respective changes of the concentration at the effect site. All previously presented examples, for instance, are time-invariant PK/PD-models.

TIME-VARIANT MODEL

For some drugs, however, pharmacodynamic parameters like E_{max} and EC_{50} may undergo time-dependent changes, resulting in changes in effect intensities without changes in drug concentrations at the effect site. The respective models are categorized as time variant. The possible decrease or increase in sensitivity towards a stimulus is then related to as tolerance and sensitization, respectively

Tolerance is characterized by a reduction in effect intensity at concentrations that earlier produced a greater effect. The diminishing response with rechallenging stimulus may for example be caused by a decrease in the number of receptors or a decrease in the receptor affinity, both resulting in a clockwise hysteresis loop for the respective concentration-effect relationship.

Sensitization, opposite to tolerance, is characterized by an increasing response with time towards the same concentration and results in a counterclockwise hysteresis curve of the concentration-effect relationship. Thus, in general, counterclockwise hysteresis can result either from time-variant pharmacodynamics, from dispositional delays or from an indirect response mechanism.

TRIAL DESIGNS

Three different trial designs used normally are parallel, cross-over, and titration. In a parallel study design, subjects are randomized to one of several treatment options,Such a design supports the estimation of population exposure response characteristics well, but not that of individual characteristics.

In a cross-over design, each subject receives all the treatments. This is the most powerful study design for estimating the individual exposure-response relationshipsbutmay experience carry over effects from previous treatments. In the titration design patients are usually initiated at a low dose, which is then gradually increased until no additional benefit is observed, or until dose-limiting toxicity occurs.In several cases, particularly for the cross-over and titration designs, sophisticated data analysis such as mixed-effects modelling is required.Subjects may be randomized to receive a particular dose or concentration of the test drug or to a particular effect produced by the drug. They are Randomized Dose Controlled (RDCT), Randomized Concentration Controlled (RCCT), or Randomized Effect Controlled (RECT) trials. In an RDCT, the different doses of the drug to be tested are randomly administered to the subjects. Data are then collected throughout the trial and analyzed using an appropriate method. In an RCCT, a set of target drug concentration levels are selected based on the exposure response relationship established from previous studies[13]. Subjects are then randomized to one of these prespecified target concentrations. The drugs which can be used for such trial designs are those where the PK has a large unexplained variability[14] (RCCT) and those where the PD has a large unexplained variability[15] (RECT).

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PK/PD MODEL ROLE IN DRUG DEVELOPMENT

An increased use of PK/PD modeling in drug development has been accepted by industry, academics and regulatory authorities. A PK/PD-guided approach to drug development can improve the development process by enhancing the effective use of resources in preclinical and clinical development stages. The potential benefit of these relationships was important considering that similar unbound plasma concentrations often produce the same effect inexperimental animal models and humans, but doses may be different due to interspecies differences.

In clinical drug development, PK/PD-relationships defined in phase I dose escalation studies on healthy subjects provide information for the rationale design of all subsequent clinical development phases. In phase II and III, population PK/PD modelling was applied to further examine the dose concentration effect relationship in patients, as well as to elucidate and differentiate sources of interindividual variability in response. In late phase III and phase IV population PK/PD approaches are also utilized to explore and select dosage requirements in different subpopulations of patients[16].Thus, PK/PD-based concepts can be used as decision making tools for scientific and strategic decisions in all stages of drug development, leading to reductions in development cost and time.

FUTURE CONSIDERATIONS

The failure rates in drug development are very high at both, the registration trial and the regulatory review stages. Application of pharmacometric methods can enhance future development plans and reduce these attrition rates. The FDA has set a target to design 50% of all pediatric trials using simulations by 2015 and 100% by 2020. However, modeling and simulation must not be viewed as a substitute for clinical trials. The aim was simply employ these techniques into a continuous learn apply paradigm, use prior knowledge, improve trial design, and support evidence for approval and labelling of drugs.

II. CONCLUSION

Pharmacometrics plays a significant role in improving drug development. Model based drug development is the need of an hour which integrates knowledge of disease status, drug characteristics and patient features to predict the possible outcome. PK/PD models and simulations are very effective pharmacometric tools which ensure smooth passage of drug development process from preclinical to clinical phases of trials. By implementing learn apply paradigm, effective drug development process can be achieved which not only reduces the cost from clinical failures and also reduces the time for drug approval.

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