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Review

Modeling of Pharmacokinetic/Pharmacodynamic (PK/PD) Relationships: Concepts and Perspectives

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Pharmacokinetic/pharmacodynamic (PK/PD)-modeling links dose-concentration relationships (PK) and concentration-effect relationships (PD), thereby facilitating the description and prediction of the time course of drug effects resulting from a certain dosing regimen. PK/PD-modeling approaches can basically be distinguished by four major attributes. The first characterizes the link between measured drug concentration and the response system, direct link versus indirect link. The second considers how the response system relates effect site concentration to the observed outcome, direct versus indirect response. The third regards what clinically or experimentally assessed information is used to establish the link between concentration and effect, hard link versus soft link. And the fourth considers the time dependency of pharmacodynamic model parameters, distinguishing between time-variant versus time-invariant. Application of PK/PD-modeling concepts has been identified as potentially beneficial in all phases of preclinical and clinical drug development. Although today predominantly limited to research, broader application of PK/PD-concepts in clinical therapy will provide a more rational basis for patient-specific dosage individualization and may thus guide applied pharmacotherapy to a higher level of performance.

KEY WORDS: pharmacokinetics; pharmacodynamics; pharmacology; modeling.

INTRODUCTION

The basis of clinical pharmacology is the fact that the intensity of many pharmacological effects is a function of the amount of drug in the body and more specifically the concentration of drug at the effect site, the site of action. The relationship between the administered dose of a drug, the resulting concentrations in body fluids and the intensity of produced outcome may be either simple or complex, and thus obvious or hidden. However, if no simple relationship is obvious, it would be misleading to conclude a priori that no relationship exists at all rather than that it is not readily apparent (1).

For a long time, the pharmacological areas of pharmacokinetics and pharmacodynamics had been considered as separate disciplines. Pharmacokinetics was limited to the description of concentration-time courses of drugs in different body fluids, pharmacodynamics to the characterization of the intensity of effects resulting from certain drug concentrations at the assumed effect site. Simplified, classical pharmacokinetics characterized '*what the body does to the drug*,' whereas classical pharmacodynamics assessed '*what the drug does to the body*' (2).

However, the information content provided by both of these disciplines is limited if regarded in isolation. On the one hand side, pharmacokinetic studies are only meaningful if there is a known relationship between the described concentrations and the drug's effects and/or side effects. On the other hand side, pharmacodynamics only considers concentration-effect relationships without accounting for its temporal arrangement and is thus only valid under the assumption of constant concentrations at the effect site, e.g. at steady-state.

Pharmacokinetic/pharmacodynamic (PK/PD) modeling builds the bridge between these two classical disciplines of pharmacology. It links the change in concentration over time as assessed by pharmacokinetics to the in most cases static relationship between the concentration at the effect site and the intensity of observed response as quantified by pharmacodynamics (Fig. 1). Thus, the resulting so-called integrated PK-PD-models allow describing the complete time course of the desired and/or undesired effects in response to a dosage regimen.

EVOLUTION OF PK/PD

Parallel to the evolution of pharmacokinetics first attempts have been made to account for the dynamic nature of pharmacologic responses (3–6). For numerous directly and reversibly 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. However, characterization of these dose-concentration-effect relationships remained in most cases limited to drugs with a straight correlation between observed

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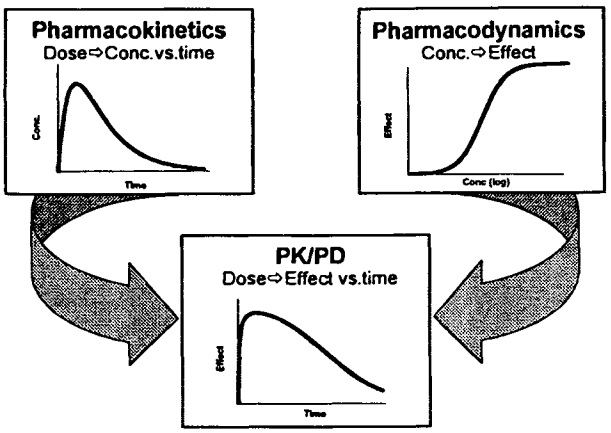

Fig. 1. Pharmacokinetic/pharmacodynamic (PK/PD) modeling as combination of the classic pharmacological disciplines pharmacokinetics and pharmacodynamics (modified from (15), reproduced with permission).

effect and measured concentration and failed if the intensity of effect lagged behind the concentrations.

This and other obstacles hindered a widespread use of PK/PD-concepts until the beginning 1980's, when PK/PD-modeling achieved a breakthrough by two major innovations. First, the temporal dissociation between effect and concentration that causes a counterclockwise hysteresis in the effect versus concentration relationship could be overcome by the effect-compartment approach developed by Sheiner and Holford (2,7). This concept facilitated to link pharmacokinetics and pharmacodynamics for a wide range of therapeutic compounds. Secondly, the often complex and time-consuming mathematical calculations associated with PK/PD-analysis techniques could be readily performed due to increasing availability of inexpensive and easy-to-use computational resources. Both factors together initiated a boost for the growth, importance and sophistication of PK/PD-modeling techniques.

MODELS' COMPONENTS

Basically, models are simplified descriptions of certain aspects of reality by mathematical means, thereby allowing to concentrate on the factors believed to be important (8,9). In case of PK/PD-modeling, the biological processes involved in the elaboration of the observed drug effect are regarded with the overall purpose to allow a quantitative description of the temporal pattern of pharmacologic effects, and, even more important, a prediction beyond the existing data.

A PK/PD-model in general consists of a pharmacokinetic model section and a pharmacodynamic model section. Although nonparametric and semiparametric models have been described (10,11), parametric modeling approaches are the most commonly used and will thus be discussed hereafter.

Pharmacokinetics

The pharmacokinetic model component provides the concentration-time course in the sampled body fluid, normally plasma, serum or whole blood (for which in the following plasma will be used as a synonym), resulting from the administered dose. Compartmental pharmacokinetic models are the most widely used for this purpose, as they provide a continuous description of the concentration that can easily serve as input function for the pharmacodynamic model portion. Since only the free, unbound concentration at the effect site is pharmacologically active, modeling of free concentrations should be preferred if any nonlinearity in plasma or tissue binding is suspected and might obscure the dose-concentration-effect relationship to be characterized (12–14).

Pharmacodynamics

The pharmacodynamic model component relates the concentration provided by the kinetic model to the observed effect. Dependent on the mechanisms involved, it may consist of one or several transduction and response elements that express the finally observed effect directly or via multiple intermediary response steps.

In its simplest form, the observed effect is directly related to the effect site concentration and the concentrations at the effect site and in plasma are in equilibrium. Under pharmacokinetic steady-state conditions, this is the case for all directly and reversibly acting drugs. In this situation, the measured plasma concentration serves as input for the concentration-effect relationship.

The classic and most commonly used pharmacodynamic model under these conditions is the sigmoid E_{max}-model, which is an empirical function for describing non-linear concentration-effect relationships. It has the general form:

$$E = \frac{E_{max} \cdot C^n}{EC_{50}^n + C^n}$$

where the effect E is a function of E_{max}, the maximum effect, C, the concentration of the drug, EC_{50}, the concentration of the drug that produces half of the maximal effect, and n, the so-called shape factor. The sigmoid E_{max}-model can be related to receptor theory. EC_{50} is the parameter characterizing the potency of the drug in the system, i.e., the sensitivity of the organ or tissue to the drug, E_{max} reflects its efficacy, i.e., the maximum response (2,15). Although n can also be derived from receptor theory as number of molecules interacting with one receptor, it is in practice merely used to provide better data fits.

Albeit the sigmoid E_{max}-model is highly versatile for different situations, several other less complex relationships have been applied under similar conditions, i.e. for direct, reversibly acting drugs with equilibrium between the concentrations at the effect site and in plasma. These models can be seen as specific cases of the sigmoid E_{max}-model and comprise the simple E_{max}-model, the log-linear model, the linear model and the fixed effect model (15,16). The preferred model in any given situation is determined by many factors including the drug used, the degree of linearity in the concentration-effect curve and the potential for achieving the maximum effect possible. However, if the defined conditions are not fulfilled, e.g., under non steady-state and for indirectly acting drugs, more sophisticated modeling approaches have to be applied as discussed hereafter.

Since PK/PD-modeling has first been developed and is most frequently applied for reversibly acting drugs with continuous effect data, the present review will focus on this kind of PK/PD-analysis. However, it should not remain unmentioned that similar concepts have also successfully been applied to

model irreversible effects of drugs like cancer chemotherapeutics (17) or antibiotics (18) as well as noncontinuous effect data like categorical or dichotomous responses, e.g., the pain relief categories resulting from ketorolac analgesia (19) or the loss of voluntary motor power as clinical endpoint during thiopental anesthesia (20).

OUTCOME MEASURES

For PK/PD-relationships, it is pivotal to identify adequate outcome measures in order to relate concentration to quantifiable effect (21). However, investigators tend to focus on those efficacy measures that are most reproducibly or conveniently to quantify, but these may bear little or no relationship to the therapeutically relevant effect (1). Hence, the importance of the appropriate choice of short-term markers predicitve of long-term clinical outcomes has repeatedly been emphasized (21–23).

Efficacy measures can be categorized as *biomarkers, surrogate markers* or *clinical outcomes*. While the clinical outcome is the ultimate efficacy measure quantifying the direct benefit to a patient, for example cure or decreased morbidity, it is often difficult to quantify. Instead, clinical outcomes are often predicted from surrogate markers that can readily and sooner be observed and can easily be quantified. The essential feature of a surrogate marker is that it predicts clinical outcome. Typical examples for surrogate markers are physiologic functions like pupil dilation in case of narcotics or biochemical markers like tumor markers in case of anticancer drugs (22). Exercise tolerance tests used in chronic stable angina are surrogates for the incidence of myocardial infarction, and indicate at the same time the degree of myocardial perfusion and patient functionality (21). Before surrogate endpoints can be used to predict clinical outcomes, however, it is crucial to validate them in accordance with good clinical practice methods. This has to include the proof of relevance, i.e., that changes in the marker are correlated to changes in disease state or outcome, as well as criteria similar to those used in analytical method validation, as repeatability, reproducibility, and sensitivity. Additionally, the assay quantifying the biochemical or physiological marker used as surrogate has to undergo the same rigid validation procedure as used for assays quantifying drug concentrations as pharmacokinetic endpoints (24,25).

Biomarkers are measurable physiological or biochemical parameters that reflect some pharmacodynamic activity of the investigated drug, even if they are not directly related to clinical outcome. They may be useful to get insight in the overall PK/PD behavior of a compound of interest. However, only if changes in biomarkers are predictive of clinical outcome, they are considered surrogate markers.

MODELING AND MODEL SELECTION

Although PK/PD-models are always a simplification of the real physiological process, they might either be purely descriptive by simply combining the observed time courses of concentration and effect neglecting the underlying physiological mechanisms involved or might be mechanism-based appreciating the physiological events involved in the elaboration of the observed effect. Since predictive, not descriptive modeling is the ultimate goal of PK/PD-analysis, mechanism-based models should be preferred as they not only describe the observations but also offer some insight into the underlying biological processes involved and thus provide flexibility in extrapolating the model to other clinical situations (2). The increasing use of mechanism-based instead of "black box" approaches moves PK/PD-modeling, according to Levy (26), "from abstract number crunching to a physiologic mechanism-orientated endeavor."

The pharmacokinetic and pharmacodynamic data as well as the link between them can either be modeled separately or simultaneously (8). Since in most cases the pharmacokinetic model is better understood than the pharmacodynamic model, a subsequent, stepwise modeling approach is often preferred, thereby avoiding pitfalls due to poor pharmacodynamic data or a wrong model selection that might otherwise be obscured. However, for both, mechanism-based as well as descriptive models, the validity has to be tested thoroughly under different conditions, e.g., different dosing regimens and different routes of administration. Only rigorous validation procedures can ensure dose- and time-independence of pharmacodynamic parameters like E_{max} and EC_{50} and are thus necessary before the modeling approaches can be applied for predictive rather than descriptive purpose (27).

CLASSIFICATION OF PK/PD-MODELS

Integrated PK/PD-models can be classified according to the manor in which the measured pharmacokinetic and pharmacodynamic data are related to each other. Four attributes have been proposed that might be used to distinguish between different basic modeling concepts (15). 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 information used to relate concentration to effect, and the time-dependency of the parameters used in the pharmacodynamic model component (Fig. 2). The resulting alternatives are:

- 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

While the measurement of drug concentrations is usually performed in plasma, the input in the response system mediating

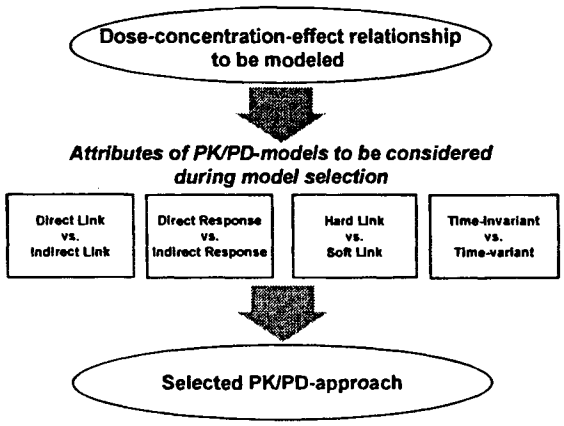

Fig. 2. Four basic attributes characterizing PK/PD-models (modified from (15), reproduced with permission).

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 an 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

For direct link models, the measured concentration in plasma is directly linked to the effect site concentration. 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. Hence, the measured concentrations can directly serve as input function in the pharmacodynamic model component, thereby directly linking measured concentration to the observed effect (Fig. 3a). 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 (see following paragraphs).

An example for a direct link model was provided by Racine-Poon et al. 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 E_{max}-model (Fig. 4) (28). Auler *et al.* used a similar approach to link analgesia quantified by a visual analogue scale to the plasma concentration of diclofenac (29).

Indirect Link

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 modeled peripheral compartment concentration profile may serve as input function for the pharmacodynamic model component (Fig. 3b).

Hochhaus *et al.* related the pulmonary and cardiac effects of fenoterol to the concentration profile in the shallow peripheral

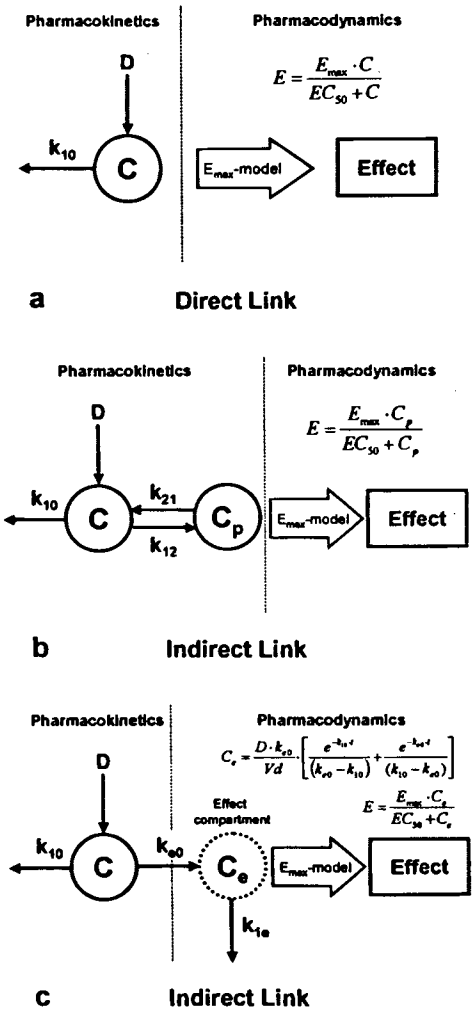

Fig. 3. Direct link versus indirect link models. (a) Direct link between measured concentration C and observed effect. Indirect link between measured concentration C and observed effect, either (b) via the concentration in a peripheral pharmacokinetic compartment C_p or (c) via a hypothetical effect compartment concentration C_e. D is the dose and k_{10}, k_{12}, k_{21}, k_{e0}, and k_{1e} are first order rate constants. The effect is mediated by an arbitrarily chosen E_{max}-model.

compartment of a three-compartment model by applying a sigmoid E_{max}-model (30). Similarly, Kramer *et al.* quantified the inotropic effect of digoxin as change in the electromechanical systole corrected for heart rate, and related it via an E_{max}-model to the concentration in one of the tissue compartments of a mammillary three-compartment body model (31), although an indirect response model might be more appropriate considering newer results on the mechanism of action of digoxin. The possibility to use drug concentrations in peripheral pharmacokinetic compartments as effect site concentration, however, seems to be the exception rather than the rule, and there is no a priori reason to expect this relationship to occur (2).

A more general approach for an indirect link between concentration and effect was introduced by Holford & Sheiner (2,7,8) based on the groundwork of Segre (32). The conceptual advance of this so-called effect-compartment model was the realization that the time course of the effect itself can be used to define the changes in concentration at the effect site and

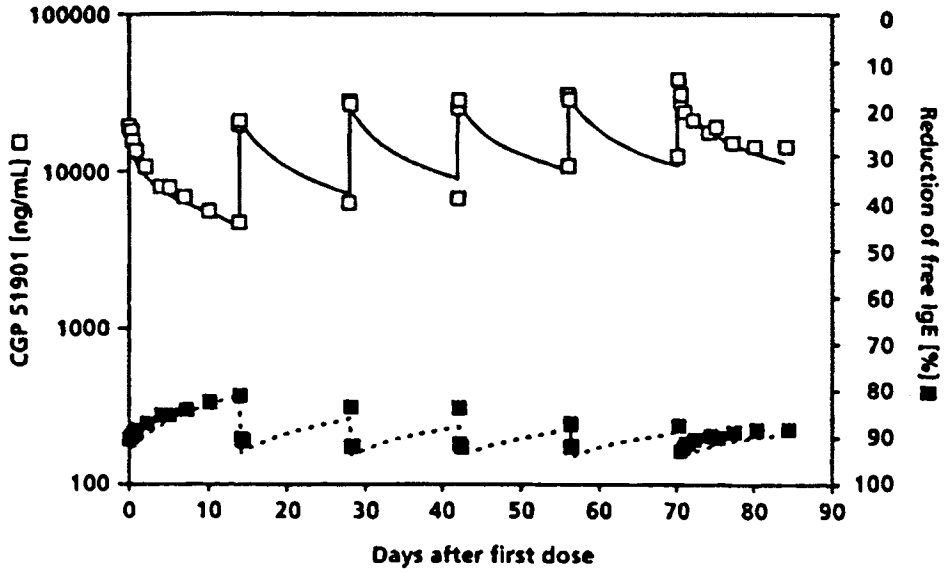

Fig. 4. Observed (□) and predicted (——) serum concentration of the anti-human IgE antibody CGP 51901 and observed (■) and predicted (----) reduction of free IgE in one representative patient, given six doses of 60 mg biweekly. The predictions are modeled with a direct link model (modified from (28); reproduced with permission).

thereby leading to a collapse of the hysteresis loop in the 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 (Fig. 3c). Since the drug influx into the effect compartment is assumed to follow a first-order process but the received mass is negligible compared to the pharmacokinetic model, the influx rate is also negligible. Thus, the equilibration process between plasma and effect site is only determined by the first order rate constant k_{eo} that describes the loss of drug from the effect compartment and is not directed towards any of the pharmacokinetic compartments.

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 (33).

Examples for the application of the effect-compartment approach were given by Dingemanse *et al.* for the EEG effects of the short-acting benzodiazepine Ro 48-6791 (Fig. 5) (34) as well as by Salazar *et al.* for the relationship between the plasma concentration of d-sotalol and its electrophysiological activity quantified as QTc interval prolongation (35). Both authors used mammillary multi-compartment pharmacokinetic models with the effect compartment attached to the central compartment and the effect mediated via a sigmoid E_{max}-model.

DIRECT RESPONSE VERSUS INDIRECT RESPONSE MODELS

Dependent on the involved physiological mechanisms, the expression of the observed effect might either be directly related

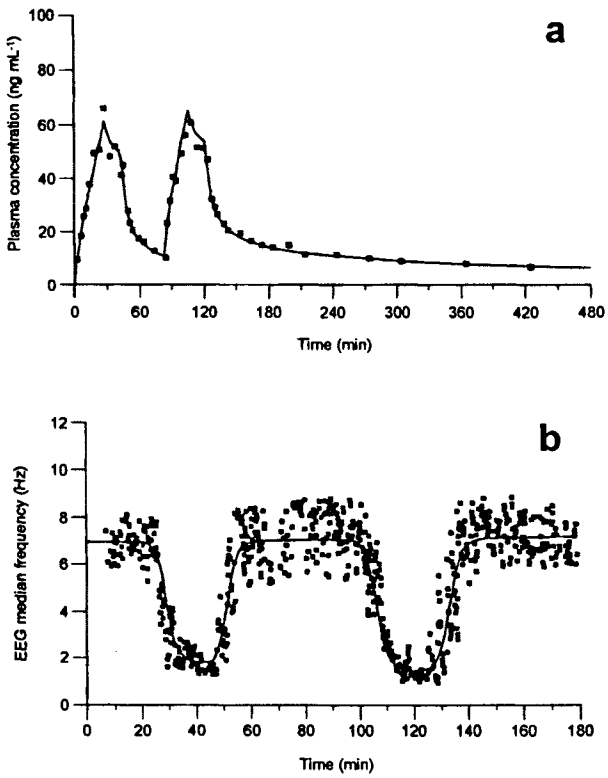

Fig. 5. (a) Actual (■) and fitted (——) plasma concentration profile and (b) resulting actual (■) and fitted (——) median EEG frequency in a representative elderly subject after two infusion cycles with the short-acting benzodiazepine Ro 48-6791. The predictions are modeled with an effect compartment model as typical indirect link model (modified from (34); reproduced with permission).

to the concentration at the effect site or might be secondary to one or several intermediary response steps.

Direct Response

For direct response models the observed effect is determined 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 consequently also represent direct response models (28,29). 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 (30,31,34,35).

Indirect Response

Aside 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 counterclockwise 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 can not be attributed to distributional process, mechanism-based indirect response models should be applied.

Indirect response modeling was first introduced by Nagashima *et al.* for the anticoagulant effect of warfarin mediated by a change in the prothrombin complex activity synthesis rate (36). This concept was later on elaborated by Dayneka et al. proposing four basic models for indirect pharmacodynamic response (37,38). Fig. 6 illustrates the general approach where the rate of change in response is controlled by a zero order process (zero order rate constant k_{in}^0) for production of the response and a first order process (first order rate constant k_{out}) for loss of the response. The response itself can then be modulated through the effect site concentration by either stimulating or inhibiting k_{in}^0 (Fig. 6a) or k_{out} (Fig. 6b) via an E_{max}-model.

Further generalization of the indirect response concept has subsequently been suggested (39,40) and a strategy for selecting the appropriate modeling approach in case of a delay between the time courses of effect and concentration, i.e., for the choice between indirect link and indirect response models, has been proposed (41).

Indirect response modeling has been applied for numerous drugs, especially in cases where endogenous substances are involved in the expression of the observed response. Rohatagi *et al.* used an indirect response model to characterize the suppression of the hypothalamic-pituitary-adrenal (HPA) axis by the corticosteroid fluticasone propionate (42). Endogenous cortisol plasma concentrations as marker of HPA-activity in this model were determined by a circadian rhythm of cortisol release and a first-order elimination process, and cortisol suppression was modeled by inhibition of the release rate dependent on the fluticasone propionate plasma concentrations (Fig. 7).

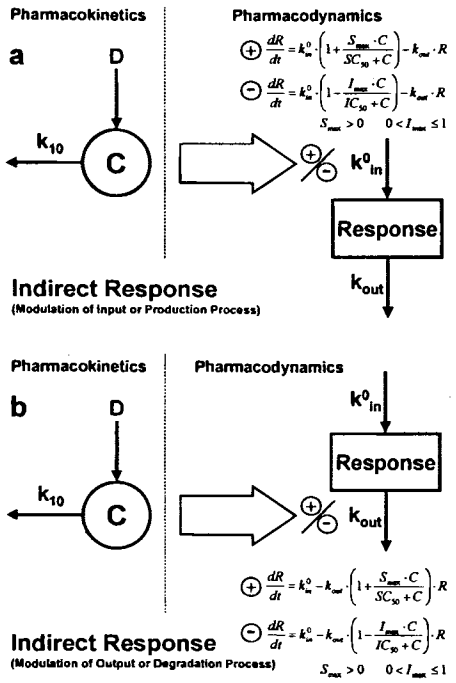

Fig. 6. Indirect response models. Indirect modulation of the response by stimulating or inhibiting (a) the production process (zero-order production rate constant k_{in}^0) or (b) the degradation process (first-order degradation rate constant k_{out}). D is the dose, C the concentration in plasma, and k_a and k_{10} are first order rate constants in the arbitrarily chosen one-compartment model.

Jusko *et al.* applied an indirect response model to characterize the muscular response in patients with myasthenia gravis during pyridostigmine therapy. Acetylcholine levels in the neuromuscular junction were used as intermediate response element and were modulated by pyridostigmine dependent inhibition of acetylcholine inactivation by acetylcholine esterase (43).

The concept of indirect response mechanisms could also be expanded to the modeling of more complex receptor/gene mediated effects as shown for the induction of the hepatic enzyme tyrosine aminotransferase by glucocorticoids using a cascade of combined indirect response models for the different physiological steps involved (44,45).

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 (46).

Soft Link

Soft link models typically utilize both measured data sets, concentration and effect, to define the link function between pharmacokinetics and pharmacodynamics. Thus, the flow of used information is bidirectional (Fig. 8a) and the link, e.g., an effect compartment, works as a buffer element accounting 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 for hysteresis in the concentration-effect relationship without further consideration

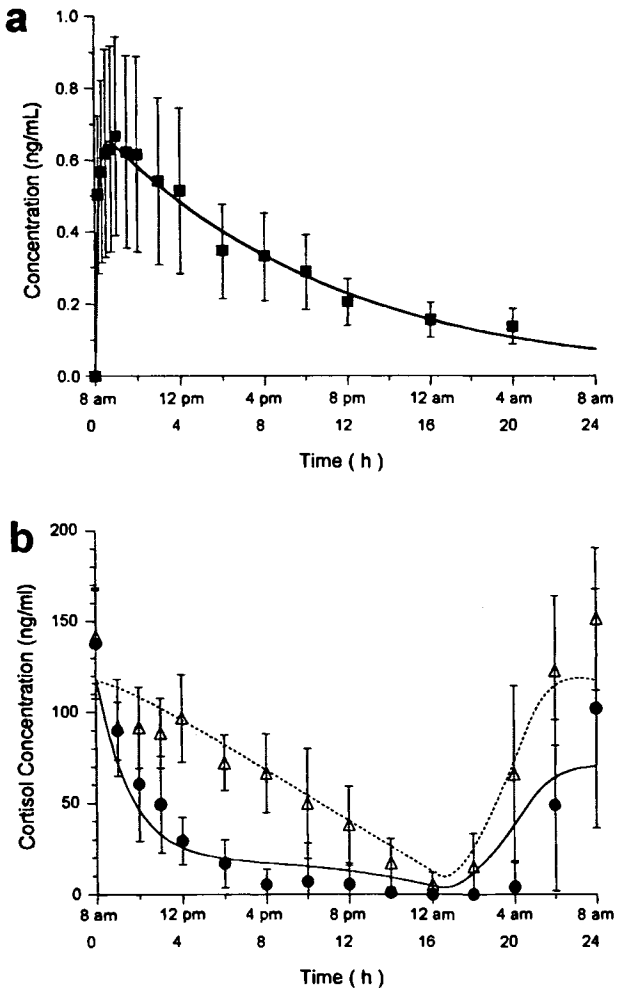

Fig. 7. Measured (points; mean ± SD) and modeled (lines) plasma concentration-time profiles of (a) fluticasone propionate and (b) resulting endogenous cortisol (●; versus baseline Δ) in 12 subjects after inhalation of 2000 μg fluticasone propionate. The cortisol suppression induced by fluticasone propionate was modeled with an indirect response model (modified from (42), reproduced with permission)).

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.

Hard Link

In 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. 8b). Utilized additional information comprise *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 without individual pharmacodynamic calibration

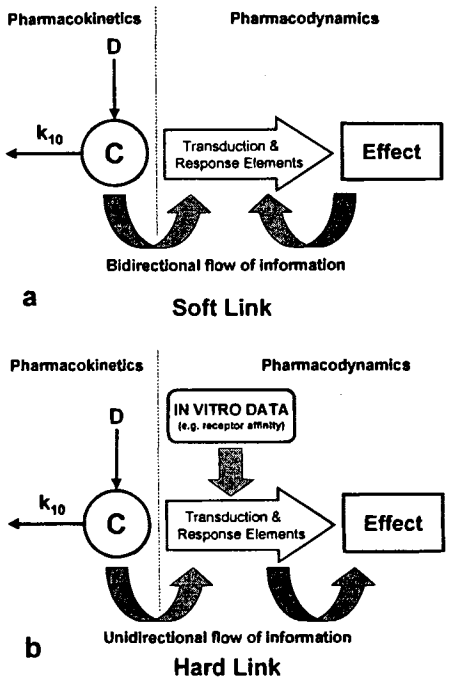

Fig. 8. Soft link versus hard link models. (a) Soft link approach using concentration and effect data to define the link in between. (b) Hard link approach using concentration data and additional mechanism-based *in vitro* information to define the link and predict the effect.

solely based on the pharmacokinetic data and *in vitro* measurements.

The hard link approach has been successfully applied in PK/PD-models for different effects of corticosteroids, where it could be shown that the EC_{50} based on free steroid concentration is comparable to IC_{50}-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 (46). A similar approach was used by Nix *et al.* to model the pharmacodynamic interaction between the antibiotics cefotaxime and ofloxacin where the pharmacodynamic target parameter area under the inhibitory-time curve (AUIC) was predicted based on serum concentrations and inhibitory titers in serum ultrafiltrate for different bacteria (18).

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

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

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 (Fig. 9).

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.

Tolerance phenomena in context with PK/PD-modeling have been described by Jonkers *et al.* for the hypokaliemia resulting from the β_2-agonist terbutaline (47) and by Meibohm *et al.* for the suppression of endogenous cortisol by the corticosteroid triamcinolone acetonide during prolonged therapy (48). The first example noticed an increase in EC_{50} over time, most likely attributed to a decrease in receptor number in the presence of spare receptors, the latter one a decrease in E_{max} over time.

More complex models that include the time-dependency in the PK/PD-approach can be distinguished into three different classes. The first are models based on the implementation of a rate constant to modulate the effect system for tolerance, as for example presented by Chow *et al.* for the progressive attenuation of the chronotropic effect of cocaine (49,50). In models of the second class, tolerance development is driven by the concentration of the drug. Porchet *et al.* used this approach in modeling the cardioaccelerating effect of nicotine, thereby modulating the effect through a hypothetical, noncompetitive antagonist whose formation is driven by the concentration of the agonist nicotine (51). The third class comprises models in which tolerance development is driven by the effect of the drug, as illustrated by Bauer and Fung in their mechanism-based model for the hemodynamic tolerance towards nitroglycerin, where the counter-regulatory vasoconstrictive effect is determined by the extent of the initial nitroglycerin-induced vasodilatation (52). In addition to these classes, Wakelkamp *et al.* also applied indirect response modeling to describe the tolerance in the diuretic and natriuretic effect of furosemide (53).

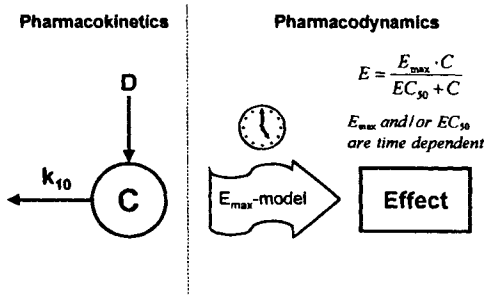

Fig. 9. Time-variant models. Time dependency of the pharmacodynamic parameters involved in mediating the effect, exemplified with an E_{max}-model and the parameters maximum effect E_{max} and concentration at half of the maximum effect EC_{50}.

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.

POPULATION PK/PD-MODELING

The usefulness and validity of PK/PD-models for the evaluation of dose-concentration-effect relationships is not limited to well-designed clinical studies with relatively small groups of individuals and frequent measurements of concentration and effect. It could also be proven for observational data obtained from large trials with sparse and imbalanced sampling schedules by applying population modeling techniques. Population PK/PD-modeling is primarily based on the nonlinear mixed effects regression models introduced by Sheiner and coworkers and allows to characterize dose-concentration-effect relationships in populations rather than individuals (54,55), thereby providing the opportunity to identify and account for sources of interindividual pharmacokinetic and/or pharmacodynamic variability. The PK/PD-concepts described in the previous paragraphs are generally also applicable in population models, and are in most cases merely expanded by inclusion of statistical models to account for the different sources of variability. Population PK/PD-modeling has successfully been applied for numerous drugs (17,62) and its concepts and application have been discussed elsewhere in detail (54–57).

RELEVANCE FOR DRUG DEVELOPMENT

An increased use of PK/PD-modeling concepts in drug development has repeatedly been promoted by industry as well as academia and regulatory authorities (57–59). A PK/PD-guided approach to drug development can streamline the development process by enhancing the effective use of resources in numerous preclinical and clinical development stages (23,65).

Evaluation of dose-concentration-response relationships already in preclinlical drug development in animal models allows obtaining potency and intrinsic activity of drugs on the basis of concentrations rather than dose, thereby accounting for pharmacokinetic differences between various compounds. The potential benefit of these relationships becomes obvious considering that similar unbound plasma concentrations often produce the same effect in experimental animal models and humans, but doses may be different due to interspecies differences (61). Thus, PK/PD-models often allow successful extrapolation of preclinical results in order to predict effective and toxic drug concentrations for clinical investigations (60).

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, especially in identifying effective and safe dosage regimens before large clinical trials are started (61). In phase II and III, population PK/PD-modeling is frequently 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 (23,57). Additionally, thoroughly defined PK/PD-relationships provide the backbone for clinical trial simulations as evolving discipline in pharmacometrics aimed to optimize clinical trial design (63,64).

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 optimized experimental design and thus reductions in development cost and time (23,60). Although several examples for the beneficial application of PK/PD-concepts and its resulting time savings in drug development have been provided (23,66), additional investigations on its economic benefits are urgently needed to consolidate its role in the development process and to provide motivated preclinical and clinical pharmacologists with evidence to convince decision makers of its merits.

SUMMARY AND OUTLOOK

Although today predominantly still limited to drug development and research, PK/PD-modeling concepts are gaining increasing importance in drug dosing and applied pharmacotherapy. Expansion of the classical therapeutic drug monitoring services from simple plasma concentration monitoring to more complex PK/PD-based dosage individualization has been proposed (65) and seems at least for specific patient subgroups desirable. Thus, the concepts of PK/PD-modeling are likely to be introduced, transferred and applied in clinical praxis to predict time courses of clinical outcome and provide a more rational basis for patient-specific individualized dosing. The widespread appreciation and increasing application of modeling PK/PD relationships in industry, academia and clinic will in future not only optimize applied pharmacotherapy as well as accelerate the drug development process, but it will also provide a profound impetus to reshape goals and mission of clinical pharmacology at its transition into the new millenium.

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