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Basic concepts of pharmacokinetic/ pharmacodynamic (PK/PD) modelling

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Abstract. Pharmacokinetic (PK) and pharmacodynamic (PD) information from the scientific basis of modern pharmacotherapy. Pharmacokinetics describes the drug concentration-time courses in body fluids resulting from administration of a certain drug dose, pharmacodynamics the observed effect resulting from a certain drug concentration. The rationale for PK/PD-modelling is to link pharmacokinetics and pharmacodynamics in order to establish and evaluate dose-concentration-response relationships and subsequently describe and predict the effect-time courses resulting from a drug dose. Under pharmacokinetic steady-state conditions, concentration-effect relationships can be described by several relatively simple pharmacodynamic models, which comprise the fixed effect model, the linear model, the log-linear model, the E_{max}-model and the sigmoid E_{max}-model. Under non steady-state conditions, more complex integrated PK/PD-models are necessary to link and account for a possible temporal dissociation between the plasma concentration and the observed effect. Four basic attributes may be used to characterize PK/PD-models: First, the link between measured concentration and the pharmacologic response mechanism that mediates the observed effect, direct vs. indirect link; second, the response mechanism that mediates the observed effect, direct vs. indirect response; third, the information used to establish the link between measured concentration and observed effect, hard vs. soft link; and fourth, the time dependency of the involved pharmacodynamic parameters, time-variant vs. time-invariant. In general, PK/PD-modelling based on the underlying physiological process should be preferred whenever possible. The expanded use of PK/PD-modelling is assumed to be highly beneficial for drug development as well as applied pharmacotherapy and will most likely improve the current state of applied therapeutics.

Key words: pharmacology – pharmacokinetics – pharmacodynamics – modelling

Rationale for PK/PD-modelling

The rational use of drugs and the design of effective dosage regimens is facilitated by the appreciation of the relationships between the administered dose of a drug, the resulting drug concentrations in body fluids accessible for measurements, and the intensity of pharmacologic effects caused by these concentrations [Gibaldi et al. 1971]. These relationships and thus the dose of a drug required to achieve a certain effect is determined by its pharmacokinetic and pharmacodynamic properties.

Pharmacokinetics describes the time course of the concentration of a drug in a body fluid, preferably plasma or blood, that results from the administration of a certain dose. In simple words, pharmacokinetics is *'what the body does to the drug'*. Pharmacodynamics describes the intensity of a drug effect in relation to its concentration in the body fluid. It can be simplified to *'what the drug does to the body'* [Holford and Sheiner 1982].

Pharmacokinetic/pharmacodynamic (PK/PD)-modelling combines both approaches and tries to establish models in order to describe the effect-time course directly resulting from the administration of a certain dose (Figure 1). Thus, a so-called integrated PK/PD-model consists of a pharmacokinetic model component that describes the time course of a drug in some body fluid and a pharmacodynamic model component that relates the concentration in this fluid to the drug effect.

Models in general are simplified descriptions of true biological process and can be used for data reduction and interpolation, but their major value is derived from their ability to extrapolate relationships beyond the existing data. In the case of PK/PD-models, that means to extrapolate dose-effect relationships for example from single to multiple dosing situations or from intravenous to oral or other administration routes.

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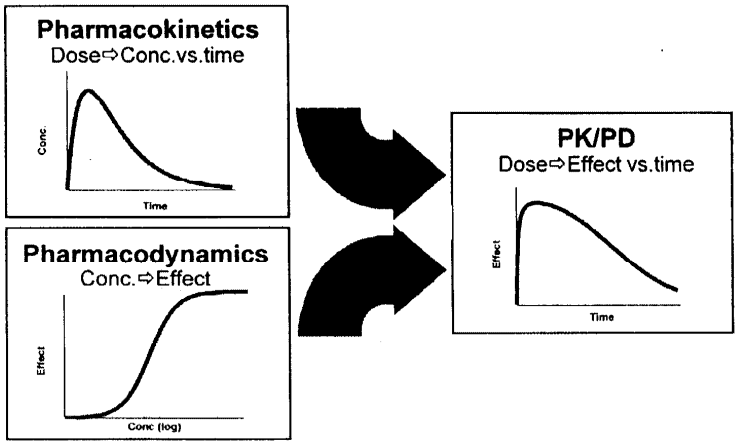

Fig. 1 Interrelationship between pharmacokinetics, pharmacodynamics and PK/PD-modelling.

Evolution of PK/PD-modelling

Early in the evolution of pharmacokinetics, relationships between drug disposition and pharmacologic effect have been described [Gibaldi and Levy 1972, Gibaldi et al. 1971, Levy 1964, Wagner 1968]. It could be shown that the intensity and time course of action of numerous directly and reversibly acting drugs are related to and largely determined by the time course of drug concentrations in the body. When the concentration-time courses and the concentration-effect relationships of these drugs were known, it was often possible to predict the temporal pattern of their pharmacological effects, including maximum intensity and duration of action.

However, for many other drugs, it was believed that there is no relationship between the drug concentration in plasma and the time course of action, predominantly based on the observation that the pharmacologic effect of many drugs lags behind their concentration in plasma. Pharmacologic effects often increase in their intensity despite decreasing drug concentrations and may persist well beyond the time, when drug concentrations in plasma are no longer determinable. As a consequence plasma concentration vs. effect plots show a more or less pronounced hysteresis.

The apparent dissociation between drug concentration and effect was first overcome by Sheiner and co-workers [Holford and Sheiner 1982, Sheiner et al. 1979] based on the concepts of Segre [1968] who proposed to use a hypothetical effect compartment to account for the lag between concentration and response, which is described in detail in one of the following sections of this paper. This approach led to a collapse of the hysteresis loop for drugs with a temporal delay between effect and plasma concentration by plotting the effect intensity versus the concentration in the effect compartment. All of a sudden, the delay between the time courses of drug concentration and effect made sense [Levy 1994].

Since then, PK/PD-modelling has exponentially evolved as a research area with increasing importance and dedication in academia, industry and regulatory authorities. The present paper aims to give a short overview over the basic concepts in pharmacokinetic/pharmacodynamic modelling and provide some structural information for classification of the applied approaches.

Pharmacokinetic models

The plasma concentration-time course of a drug is determined by the pharmacokinetic processes of distribution, metabolism and excretion as well as absorption in case of nonsystemic administration. The currently used pharmacokinetic models can basically be distinguished into compartmental, physiological and statistical models.

Although nonparametric and physiologically based pharmacokinetic models have been used as a basis for PK/PD-approaches [Holford et al. 1994, Unadkat et al. 1986, Veng-Pedersen and Gillespie 1988], compartmental models are the most frequently preferred, probably due to the fact that they provide a continuous concentration-time profile in a body fluid that can be related to a continuous effect-time profile and that the popular effect compartment concept can easily be implemented. Thus, the present paper will focus on PK/PD-modelling based on compartmental pharmacokinetic models.

Pharmacodynamic models for steady-state situations

Pharmacodynamic analysis involves quantifying drug concentration/effect relationships. Ideally, concentrations should be measured at the effect site, the site-of-action or biophase, where the interaction with the respective bio-

logical receptor system takes place, but this is in most cases not possible. Thus, concentrations in easily accessible body fluids like plasma or blood are frequently used to establish these relationships under the assumption, that the pharmacologically active, unbound concentration at the effect site is directly related to the one in the respective body fluid and that they are, under pharmacokinetic steady-state conditions, in equilibrium. Since the same proportionality holds for different steady-state plasma levels, steady-state plasma concentrations may serve as the only determinant of the observed effect.

A drug effect can be defined as any drug-induced change in a physiological parameter when compared to the respective predose or baseline value. The baseline value is the value of the same physiological parameter in the absence of drug dosing. Baseline values do not necessarily have to be constant but can change, e.g. as a function of time of day or of food intake. Furthermore, the term effect has to be clearly separated from the term efficacy. Efficacy is the sum of all therapeutically beneficial drug effects and is the most relevant target parameter in PK/PD-modelling. However, in many PK/PD-studies, efficacy is difficult to quantify and thus, easily accessible surrogate markers as effect parameters are used instead. In these cases, it is necessary to present evidence that the pharmacodynamic effect parameter used correlates with the desired efficacy to provide valid results.

For steady-state conditions, the most commonly used pharmacodynamic models are the

- fixed effect model,
- linear model,
- log-linear model,
- E_{max}-model, and
- sigmoid E_{max}-model.

Fixed effect model

A fixed effect model, also known as quantal effect model, is a statistical approach based on a logistic regression analysis. It relates a certain drug concentration with the statistical likelihood of a predefined, fixed effect to be present or absent.

The simplest case of a fixed effect model is a threshold model, where the effect E_{fixed} occurs after reaching a certain threshold concentration $C_{threshold}$, as for example described for the ototoxicity occurring during gentamicin therapy with trough levels exceeding 4 µg/ml for longer than 10 days of therapy [Mawer et al. 1974]:

$$E = E_{fixed} \quad \text{if} \quad C \geq C_{threshold} \qquad \text{(Eq. 1)}$$

where E is the measured effect and C is the measured concentration.

Since the threshold concentration will vary among patients, the probability of the effect to be present at a certain concentration will be a function of the threshold concentration distribution in the population. For example, at a digoxin plasma concentration of 2.0 ng/ml there is a 50% probability to observe digoxin toxicity, whereas at a concentration of 4.1 ng/ml the probability is 90% [Beiler et al. 1971, Holford and Sheiner 1982]. 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.

Linear model

The linear model assumes a direct proportionality between drug concentration and drug effect, as shown by Weaver et al. [1992] for the correlation of salivary flow rate and plasma concentration after pilocarpine infusions:

$$E = m \times C + E_0 \qquad \text{(Eq. 2)}$$

where E_0 is the baseline effect in the absence of drug and m a proportionality factor, that characterizes the slope of a plot of effect E versus concentration C. Although the linear model is the one that intuitively is the most popular, it rarely applies.

Log-linear model

A much more common situation than the linear model is the log-linear model with

$$E = m \times \log C + b \qquad \text{(Eq. 3)}$$

where m and b are slope and intercept in a plot of effect E versus the logarithm of the concentration C. Although b should have the unit of the effect, it is an empiric constant that has no real physiologic meaning, especially not that of a baseline value. The log-linear model is applicable in many situations and can be considered a special case of the E_{max}-model, regarding the range between 20% to 80% of E_{max}, where effect E and logarithm of the concentration C follow a linear relationship. Nagashima et al. [1969] for example used it to relate the synthesis rate of prothrombin complex activity to the plasma concentration of warfarin.

E_{max}-model

In the maximum effect E_{max}-model, concentration C and effect E are related as

$$E = \frac{E_{max} \times C}{E_{50} + C} \qquad \text{(Eq. 4)}$$

where E_{max} is the maximum effect possible and E_{50} is the concentration that causes 50% of E_{max}. E_{max} refers to the intrinsic activity of a drug, E_{50} to its potency. Lalonde et al. [1987] gave an example for applying the E_{max}-model

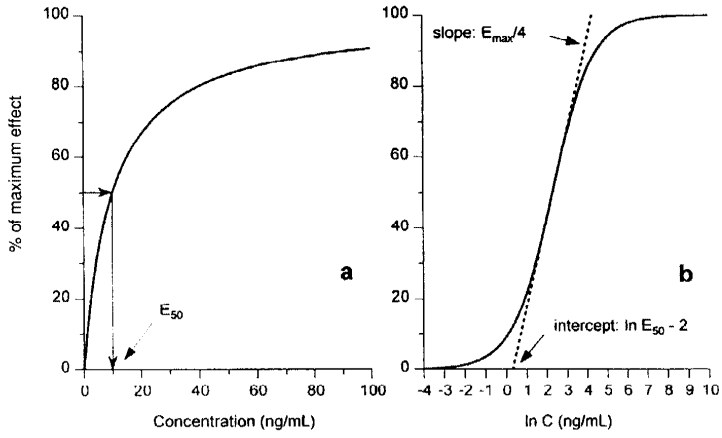

Fig. 2 Concentration-effect relationship resulting from a pharmacodynamic E_{max}-model, where the effect is either plotted against the concentration (a) or the logarithm of the concentration (b), the last resulting in the classical sigmoidal shape. [E_{max} = maximum effect, E_{50} = concentration at 50% of E_{max}].

by describing the relationship between propranolol plasma concentrations and the resulting decrease in heart rate.

The equation of the E_{max}-model (Eq. 4) is based on the receptor theory relationship [Ariens and Simonis 1964] that can be derived for the equilibrium interaction of a drug (D) with its site of action (R), e.g. a receptor, enzyme or ion channel, producing the effect E:

$$[D]+[R]\Leftrightarrow[DR]\mapsto Effect \quad \Rightarrow \quad [DR]=\frac{[R_{tot}]\times[D]}{K_d+[D]} \qquad \text{(Eq. 5)}$$

where K_d is the equilibrium constant and R_{tot} the total number of interaction sites. Under the assumption, that the observed effect E is directly proportional to the number of occupied interaction sites DR, Eq. 4 and Eq. 5 are equivalent indicating that maximum effect would be observed if all interaction sites are occupied. K_d is the concentration at which half of the interaction sites are occupied and, hence, equivalent to E_{50}.

The E_{max}-model describes the concentration-effect relationship over a wide range of concentrations from zero effect in the absence of a drug to the maximum effect at concentrations much higher than E_{50} ($C >> E_{50}$). In the presence of a baseline effect E_0, this term can simply be added to Eq. 4 as shown in Eq. 6:

$$E=E_0+\frac{E_{max}\times C}{E_{50}+C} \qquad \text{(Eq. 6)}$$

The clear non-proportional concentration-effect relationship of the E_{max}-model is presented in Figure 2 as linear and semilogarithmic plot. Whereas small increases in concentration may result in significant increases of the effect for low concentrations, this is much less pronounced for higher concentrations where only small changes in effect will result from changes in concentration. From the semilogarithmic presentation, it is apparent that in the range from 20% to 80% of the maximum effect, the relationship between effect and the logarithm of the concentration is linear. This is consistent with the log-linear model (Eq. 3). The slope of the linear phase can be calculated as $E_{max}/4$, the respective x-intercept as $\ln E_{50} - 2$, and the y-intercept b as $E_{max} \times (2 - \ln E_{50})/4$, [Hochhaus and Derendorf 1995]. At concentrations below 20% and above 80% of the maximum effect the E_{max}-model clearly deviates from the log-linear model. For concentrations much smaller than E_{50} ($C << E_{50}$), it reduces to a linear model with a slope m of E_{max}/E_{50}. Hence, both, the log-linear as well as the linear model may be interpreted as special case of the E_{max}-model.

The E_{max}-model presented in Eq. 4 assumes an increase of the effect with increasing concentrations, i. e. a stimulated effect. Opposite, inhibitory effects can be described by Eq. 7:

$$E=E_0-\frac{E_{max}\times C}{E_{50}+C} \qquad \text{(Eq. 7)}$$

where E_0 is the baseline effect. If the maximum effect E_{max} is complete suppression of the baseline effect E_0, Eq. 7 simplifies to Eq. 8:

$$E=E_0\times\left(1-\frac{C}{E_{50}+C}\right) \qquad \text{(Eq. 8)}$$

In accordance with the receptor theory the E_{max}-model also allows to describe more complex concentration-effect relationships, e. g. competitive or noncompetitive agonist and antagonist interactions at the response system, if appropriately modified E_{max}-equations are applied. This was shown by Braat et al. [1992] for the com-

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