Chapter 4

DOSE OPTIMIZATION BASED ON PHARMACOKINETIC-PHARMACODYNAMIC MODELING

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INTRODUCTION

In recent years, pharmacokinetic-pharmacodynamic relationships have received considerable attention since it was realized that they provide a causative link between drug delivery and/or drug dosing and therapeutic outcome. A drug in a certain dosage form is administered to a patient with a certain dosing schedule. This results in a certain concentration profile at the sites of effect and side effect which is the reason for the observed drug-induced changes in the patient. Pharmacokinetic-pharmacodynamic modeling (PK-PD modeling) is an attempt to quantify these relationships with the goal to explain observed phenomena and derive an optimum dosing recommendation. The questions that are to be answered are

- What is the best dose?
- What is the best dosing regimen?
- What is the best route of administration?
- What is the best dosage form?

Pharmacokinetics can be looked at as "what the body does to the drug", whereas *pharmacodynamics* is "what the drug does to the body". Pharmacokinetics describes the relationship between drug and metabolite concentrations and time. Pharmacodynamics describes the relationships between pharmacological effects and drug and/or metabolite concentrations. Combination of these two areas, PK-PD modeling, leads to the therapeutically most relevant relationship between pharmacological effects and time (Figure 1).

Whereas pharmacokinetics is an established routine discipline with widely accepted principles, pharmacodynamics is still an emerging field with many open questions. One reason for the delay in this development was the lack of techniques that allowed reproducible measurement of drug effects over time. 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 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 modeling. However, in many PK-PD studies there is little evidence if the pharmacodynamic effect parameter used has any correlation to the desired efficacy and is a validated surrogate marker.

PHARMACODYNAMIC MODELS

At present, the most commonly used pharmacodynamic models are the

- Fixed effect model
- Linear model
- Log-linear model
- E_{max} model
- Sigmoid E_{max} model

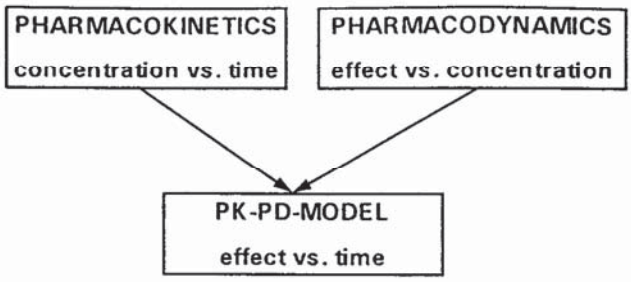

FIGURE 1. Schematic relationship between pharmacokinetics, pharmacodynamics, and PK-PD modeling.

FIXED EFFECT MODEL

A fixed effect model is a statistical approach that, for a certain drug concentration, quantifies the likelihood of a defined effect to be present or not. 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%.[1] This approach may be useful in the clinical setting 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:

$$E = E_0 + m \cdot C \tag{1}$$

where E is the effect measured, C the drug concentration, E_0 the baseline effect, and m a proportionality factor. The linear model is the one that intuitively is the most popular, although it rarely applies. One problem is that in today's educational system much emphasis is given to pharmacokinetic principles where dose-proportional changes in drug concentrations are very common. This concept is sometimes inappropriately applied to pharmacodynamic predictions expecting dose-proportional changes in drug effects.

LOG-LINEAR MODEL

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

$$E = m \cdot \log C + b \tag{2}$$

where m and b are the slope and intercept of a plot of effect E vs. the logarithm of the concentration C. This model is applicable in many situations and can be considered a special case of the E_{max} model.

E_{max} MODEL

In the E_{max} model, concentration and effect are related as:

$$E = \frac{E_{max} \cdot C}{E_{50} + C} \tag{3}$$

where E_{max} is the maximum effect possible and E_{50} is the concentration where 50% of the maximum effect is observed. This equation is equivalent to the relationship that can be derived for the equilibrium interaction of a drug (D) with a site of action (R), e.g., a receptor, enzyme, or ion channel.

$$D + R \Leftrightarrow DR$$

$$K_d = \frac{[D]\cdot[R]}{[DR]} = \frac{[D]\cdot([R]_{tot} - [DR])}{[DR]}$$

$$\frac{K_d}{[D]} = \frac{[R]_{tot}}{[DR]} - 1$$

$$\frac{[DR]}{[R]_{tot}} = \frac{[D]}{K_d + [D]}$$

$$[DR] = \frac{[R]_{tot}\cdot[D]}{K_d + [D]} \tag{4}$$

In this derivation, K_d is the equilibrium constant and R_{tot} the total number of interaction sites. Hence, if the observed effect is directly proportional to the number of occupied interaction sites (DR), Equations 3 and 4 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}.

Figure 2A shows a graphical representation of the E_{max} model with the clear nonproportionality between drug concentration and effect. Whereas for small concentrations increases in concentration may result in significant increases of the effect, this is less pronounced for higher concentrations where only small changes in effects will result from changes in concentration. Figure 2B shows the semilogarithmic presentation of Figure 2A which results in the classical sigmoidal concentration-effect curves. It is also apparent that in the range between 20 and 80% of the maximum effect, the relationship between effect and the logarithm of the concentration is linear, which is consistent with the log-linear model (Equation 2). Hence, the log-linear model can be considered as a special case of the E_{max} model for the effect range from 20 to 80% of the maximum effect. The slope of this linear phase can be calculated to be $E_{max}/4$:

$$E = \frac{E_{max}\cdot C}{E_{50} + C} = \frac{E_{max}\cdot e^{\ln C}}{E_{50} + e^{\ln C}}$$

$$\frac{dE}{d(\ln C)} = \frac{E_{max}\cdot E_{50}\cdot C}{(E_{50} + C)^2}$$

$$C = E_{50}$$

$$\frac{dE}{d(\ln C)} = \frac{E_{max}\cdot E_{50}^{\,2}}{(2\cdot E_{50})^2} = \frac{E_{max}}{4} \tag{5}$$

Hence, Equation 2 can be rewritten using the parameters of the E_{max} model, as:

$$E = \frac{E_{max}}{4}\cdot \ln C + \frac{E_{max}}{4}\cdot(2 - \ln E_{50}) \tag{6}$$

This also allows calculation of the x-intercept in Figure 2B to be $\ln(E_{50}) - 2$:

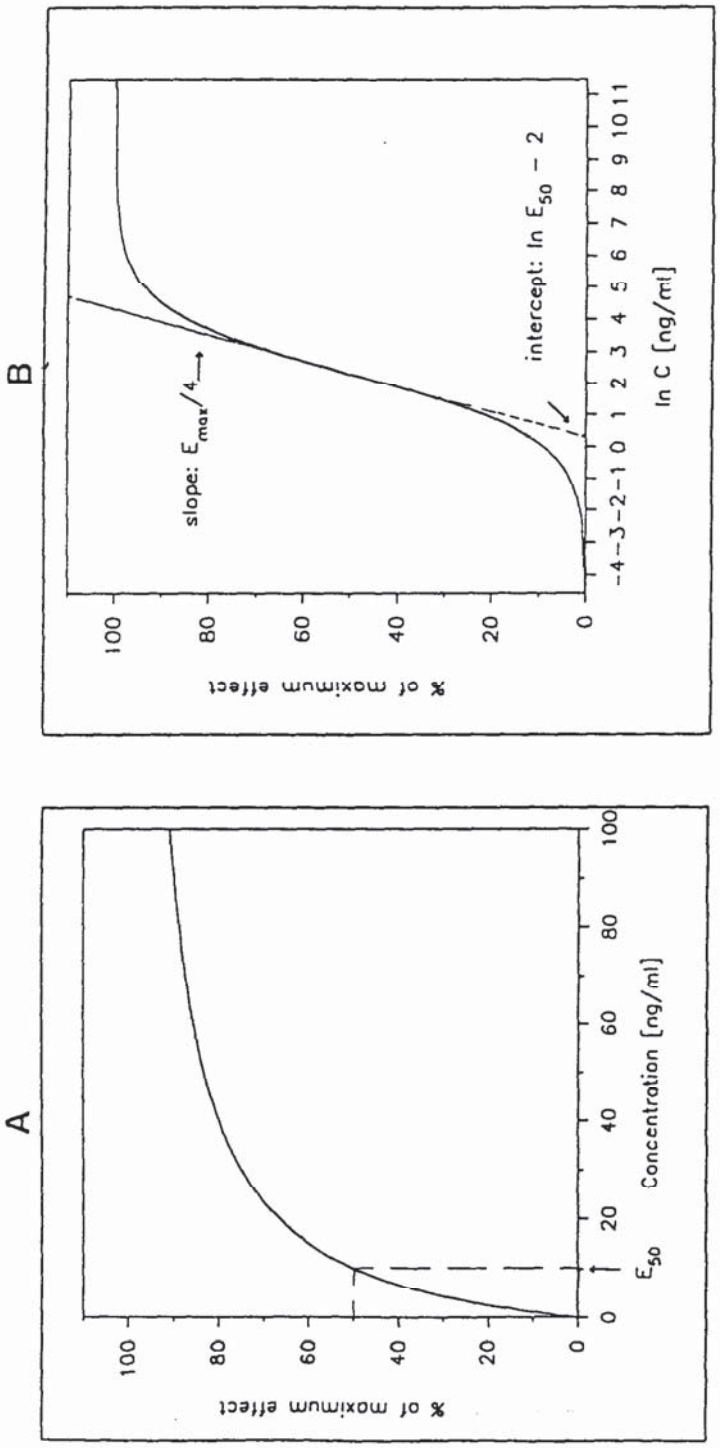

FIGURE 2. Concentration-effect relationship for the E_{max} model. (A) Normal plot; (B) semilogarithmic plot.

$$x_0 = x - \frac{y}{m}$$

$$x_0 = \ln E_{50} - \frac{E_{max} \cdot 4}{2 \cdot E_{max}} = \ln E_{50} - 2 \tag{7}$$

In the ranges below 20% and above 80% of the maximum effect the E_{max} model clearly deviates from the log-linear model.

SIGMOID E_{max} MODEL

The sigmoid E_{max} model is an expansion of the E_{max} model. Effect and concentration are related as

$$E = \frac{E_{max} \cdot C^n}{E_{50}^n + C^n} \tag{8}$$

Theoretically, this relationship can be derived to describe the interaction between n drug molecules and one interaction site in a similar way to Equation 4:

$$n \cdot D + R \Leftrightarrow D_n R$$

$$K_d = \frac{[D]^n \cdot [R]}{[D_n R]} = \frac{[D]^n \cdot ([R]_{tot} - [D_n R])}{[D_n R]}$$

$$\frac{K_d}{[D]^n} = \frac{[R]_{tot}}{[D_n R]} - 1$$

$$\frac{[D_n R]}{[R]_{tot}} = \frac{[D]^n}{K_d + [D]^n}$$

$$[D_n R] = \frac{[R]_{tot} \cdot [D]^n}{K_d + [D]^n} \tag{9}$$

However, in most cases n has no molecular basis and is merely used as an operational shape factor that allows a better data fit. This also explains why in many studies noninteger values for n are reported, which could not be possible based on the derivation in Equation 9. Figure 3 shows the effect of different values of n on the concentration-effect curves. The larger n, the steeper the linear phase of the log concentration-effect curve. It can be shown (Equation 10) that the slope is $n \cdot E_{max}/4$, hence directly proportional to n. For this reason, n is also referred to as the slope factor.

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

$$\frac{dE}{d(\ln C)} = \frac{n \cdot E_{max} \cdot E_{50}^n \cdot C^n}{(E_{50}^n + C^n)^2}$$

$$C = E_{50}$$

$$\frac{dE}{d(\ln C)} = \frac{n \cdot E_{max} \cdot E_{50}^{2n}}{(2 \cdot E_{50}^n)^2} = \frac{n \cdot E_{max}}{4} \tag{10}$$

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