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# Mechanism-based modelling of CNS drug effect: from receptor pharmacology to clinical trial

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## Abstract

The objective of pharmacokinetic/pharmacodynamic (PK/PD) modelling is to characterize and predict the time course of drug effects under physiological and pathological conditions. As such, PK/PD modelling provides the scientific basis for (i) optimization of the dosing and delivery profile of new and existing drugs, and (ii) dose adjustment in special populations. At present, PK/PD modelling is developing from a rather empirical descriptive discipline into a mechanistic science that can be applied at almost all stages of drug development. Key elements in this development are (i) the incorporation of receptor theory, and (ii) the application of dynamic systems analysis. Another important feature is characterisation of the interaction between PK/PD and disease progression. In this chapter, the development and application of mechanism-based PK/PD models is discussed for CNS active drugs with special reference to opiates and benzodiazepines. It is shown that mechanism-based PK/PD models exhibit favourable properties for extrapolation and prediction. Furthermore, it is shown that they provide a useful basis for the development, evaluation and validation of biomarkers. © 2001 Elsevier Science B.V. All rights reserved.

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# 1. Introduction

The primary objective of pharmacokinetic/pharmacodynamic (PK/PD) modelling is to identify key properties of a drug in vivo, which allows the characterisation of the time course of drug effects under physiological and pathological conditions [1]. It has been proposed that PK/PD modelling may be of value in all stages of drug development. It may

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influence decision-making at key transition steps, and thereby, rationalize and enhance the efficiency of this process. In particular, it may be helpful to identify effective and safe dosage regimens before large clinical trials [2,3].

At present, PK/PD modelling is developing from rather empirical descriptive discipline into a mechanistic science. A key element in this development has been the incorporation of receptor theory [4].

Traditionally, in PK/PD modelling empirical models such as the Hill equation have been used to describe drug concentration–effect relationships in vivo. These empirical models, however, provide only limited insight in the underlying factors that determine the shape and the location of the concentration effect curve. For example, the potency (EC<sub>50</sub>) of a compound depends on both receptor affinity and efficacy. Likewise, intrinsic activity ( $E_{max}$ ) is a function of both compound (intrinsic efficacy) and system (receptor density and the function relating receptor occupancy to pharmacological effect) characteristics (Fig. 1). For this reason, classical receptor theory combines two independent parts to describe drug action: (i) an agonist-dependent part incorporating agonist affinity and intrinsic efficacy, and (ii) a tissue (or system)-dependent part, determined by receptor concentration and the nature of the stimulus–effect relation [5].

The "operational model of agonism" is a pharmacodynamic model, which describes the pharmacological effect in terms of agonist concentration, and which explicitly takes into account the distinction between the drug-specific and the system-specific part of drug action.

$$E = \frac{E_{\rm m} \tau^n [A]^n}{\left(K_{\rm A} + [A]\right)^n + \tau^n [A]^n}$$

In this equation, E is the response,  $E_{\rm m}$  is the maximum response achievable in the system,  $\tau$  is the transducer ratio as a measure of the efficiency of transduction of occupied receptors

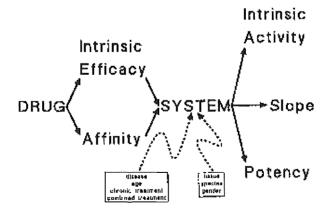


Fig. 1. The pharmacodynamic characteristics of a drug (potency, intrinsic activity, and slope of the concentrationeffect relationship) are not only dependent on drug-specific properties but also on the properties of the biological system. Various factors (a.o. disease, age, chronic treatment, or other drugs) may change the biological system, and therefore, modify the pharmacological response. This may have important implications for the optimal dosing regimen of a drug (From Ref. [4]).

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into pharmacological effect, *n* is the slope of the transducer function,  $K_A$  is the dissociation equilibrium constant of the agonist receptor complex and [*A*] is the concentration of agonist. In the equation,  $E_m$  and *n* are true system-related parameters, whereas,  $K_A$  is a pure drug-related parameter. The efficacy parameter  $\tau$  is defined as the ratio between the receptor density [ $R_0$ ] and the midpoint location of the transducer function  $K_E$ . In this manner, it is possible to take the influence of differences in receptor reserve into account.

Recently, the operational model of agonism has been incorporated successfully in mechanism-based PK/PD models for the haemodynamic and anti-lipolytic actions of  $A_1$  adenosine agonists. Thereby, it was convincingly demonstrated that mechanism-based PK/PD models allow for the prediction of in vivo drug effects from data obtained in pharmacological in vitro experiments. Furthermore, it was shown that these models could explain and predict tissue selectivity in drug action (haemodynamic versus antilipolytic effects) [6,7]. In theory, this approach also allows for the interspecies extrapolation from laboratory animals to humans, and for the understanding and prediction of pharmacodynamic variability.

In this chapter, the development and application of mechanism-based PK/PD models is discussed for CNS-active drugs with emphasis on opiates and benzodiazepines.

# 2. Opiates

Mechanism-based PK/PD modelling of the effects of synthetic opiates has focused on interspecies extrapolation and the prediction of functional adaptation. To this end, studies were conducted in a chronically instrumented rat model. The results obtained in this model were compared to similar data obtained in man.

The PK/PD correlation of a series of synthetic opiates (i.e., fentanyl, alfentanil, sufentanil) was modelled using quantitative EEG parameters as a pharmacodynamic endpoint. In the same studies, receptor binding was determined in vitro on basis of the displacement of  $[^{3}H]$  naloxone in washed rat brain membranes. Between compounds, large differences in in vivo potency but not intrinsic activity were observed, despite wide differences in the value of the sodium-shift (= a measure of intrinsic efficacy) in an in vitro receptor preparation. Simulation on the basis of the operational model of agonism provided evidence for a large receptor reserve in the system [8]. Furthermore, an excellent correlation between in vivo potency and in vitro receptor affinity was observed. These results showed that it is possible to predict the in vivo pharmacodynamics of synthetic opiates in terms of potency and intrinsic activity on the basis of in vitro receptor bioassays.

Functional adaptation to the EEG effect of alfentanil was studied in rats by comparing the results obtained upon different modes of administration. Upon repeated administration of alfentanil in rats, a parallel shift of the concentration—effect relationship to higher concentrations was observed. Simulations on basis of the mechanism-based PK/PD model showed that this could be explained by a 40% loss of functional  $\mu$ -opioid receptors [9]. We have been able to confirm this experimentally on the basis of modelling the effect of "receptor knock-down" by pre-treatment with the irreversible  $\mu$ -opioid receptor antagonist  $\beta$ -Funaltreramine [10]. These findings illustrate the utility of mechanism-based PK/PD modelling in understanding and predicting variability in pharmacodynamics.

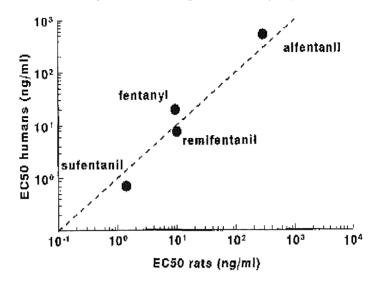


Fig. 2. Correlation between the in vivo potency  $(EC_{50})$  of different synthetic opiates in rats and humans. The dashed line represents the line if unity. The results show that on basis of mechanism-based PK/PD modelling, it is possible to predict the in vivo pharmacodynamics of synthetic opiates in terms of potency and intrinsic activity in man on the basis of data obtained in laboratory animals.

Finally, the mechanism-based PK/PD model was applied successfully to predict the in vivo potency, the new synthetic opiate remifertanil, and its major metabolite GR90291 in man on the basis of data obtained in rats (Fig. 2), thus, illustrating the utility for interspecies extrapolation of pharmacodynamics [11].

#### 3. Benzodiazepines

The pharmacodynamics of benzodiazepines has been studied using amplitudes in the 11.5-30 Hz frequency band of the EEG as a pharmacodynamic endpoint. In these studies, emphasis was on the evaluation of the validity of this biomarker as well as the extrapolation from experimental animals to humans.

In comparative studies in rats, the effects of flunitrazepam, midazolam, oxazepam, clobazam, bretazenil, flumazenil and Ro 19-4603 were compared. Thereby, wide differences in both potency ( $EC_{50}$ ) and intrinsic activity ( $E_{max}$ ) were observed [12,13]. Analysis of these data, on the basis of a mechanism-based PK/PD model, provided evidence for the lack of a significant receptor reserve in the system [14]. Receptor theory predicts that in this situation, there is a direct relationship between potency ( $EC_{50}$ ) and the affinity constant for binding to the receptor in vitro. In a separate analysis, such a relationship was indeed observed (Fig. 3) [15], confirming that amplitudes in the 11.5–30 Hz frequency band of the EEG is a relevant biomarker for the in vivo effect of benzodiazepines, reflecting modulation of GABA-ergic inhibition in a direct quantitative manner.

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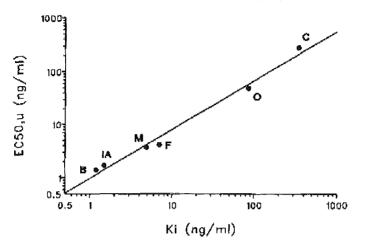


Fig. 3. Correlation (r=0.993, p<0.001) between benzodiazepine-free drug concentrations (EC<sub>50u</sub>) producing 50% of the maximal EEG effect (change in amplitude in the beta frequency band) and affinity to the central benzodiazepine receptor ( $K_1$ ). Binding to the central benzodiazepine receptor was determined on basis of displacement of [H<sup>3</sup>]-flumazenil in a washed brain homogenate at 37°C. These results show that the EEG effect is a relevant biomarker for the in vivo effect of benzodiazepines reflecting modulation of GABA-ergic inhibition in a direct quantitative manner (From Ref. [15]).

In subsequent studies, these biomarkers were applied successfully to predict the relative potency and intrinsic activity of midazolam, and its active metabolite  $\alpha$ -hydroxy-midazolam in humans on the basis of results obtained in rats [14,16].

Final investigations in this series focused on the validation of amplitude in the 11.5–30 Hz frequency band of the EEG and other parameters as a surrogate marker for the effects of benzodiazepines on sleep. To this end, investigations were performed in a panel of 21 patients with primary insomnia [17]. In these patients, the pharmacokinetic and surrogate pharmacodynamic parameters of temazepam were determined in a day-time study, following intake of a single oral dose of 10 mg. The effects on sleep were determined in a double-blind cross-over clinical trial on the basis polysomnographic sleep recording and a sleep evaluation questionnaire. The data for the effects on sleep were analyzed on the basis of a Markov Mixed effect model characterising the probability of sleep phase transition as a function of time. Between subjects a large inter-individual variability was observed in both the effects on biomarkers and the clinical improvement of sleep. Interestingly, significant correlations were observed between the effects on surrogate parameters and sleep, thus, confirming the validity of these biomarkers as a surrogate for the effect on sleep [18].

### 4. Conclusion

This chapter focuses on the development of mechanism-based PK/PD models for drugs with an effect on the central nervous system. A key element in this approach is the incorporation of receptor theory. It is shown that this kind of PK/PD models exhibits

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favourable properties for extrapolation and prediction. As such, these models can be of great value in different phases of drug development, and in particular, also the linkage of pre-clinical and clinical investigations.

It is expected that the development of mechanism-based PK/PD models will continue in the coming years. Specific elements of this development include a further incorporation of advanced receptor theory (also in relation to 'spontaneous' receptor activity and inverse agonism) and the application of dynamic systems analysis. Another important subject expected is the characterisation of the interaction with disease progression.

#### Appendix A. Discussion 7

K. Park: Was there a similar relationship between affinity and down-regulation?

**M. Danhof:** We did not look in these tolerance studies to what happened to the receptor affinity. That may also be quite difficult, because taking brains out of animals may tell us what the total number of receptors is, and it does not tell us what the efficiency of coupling is to the effective system. That is why we have taken the opposite approach by artificially knocking down the receptors to the same extent that it would give the same shift, and show it that way.

**D. Mould:** I was wondering if you have ever had a chance to apply your receptor theory to, for example, pegylated compounds? This is a situation where you are looking at reductions in affinity of the drug for the receptor as a consequence of adding polyethylene glycol to the parent molecule. However, the alterations in the molecular structure of the parent compound results in a change to the pharmacokinetics of the drug, reducing the clearance. So instead of optimising the dosage regimen, you are optimising the drug. Have you had a chance to look at that at all?

**M. Danhof:** We have never looked at it in that manner, although we have of course looked at various drugs with different affinity, which basically would be the same thing. I would expect it would be very interesting to do, and to see whether these models indeed predict that.

**A. Bye:** One of the things I would fully support is the need for the functional readouts. As my first question, what sort of functional readout can we use on a fairly continuous basis? And the second one is, we see many single-dose models published, but very few multiple-dose models published yet; to enhance sleep quality, drugs are always given in the clinic in a multiple-dose regimen.

**M. Danhof:** To begin with the last, I fully agree that we should be doing more PK/PD modelling upon the repeated dosing rather than upon single dosing: I think it is a very important issue, particularly, that also relates back basically to the tolerance development, where you basically would like to understand how the system behaves and so on. Coming back to the functional assays, I think, in general, the rating step in PK/PD modelling is much more in the area of developing realistic measures of pharmacological response rather than in the modelling process per se. If you look at the central nervous system, electrophysiology may help you to do that, I mean there are more advanced techniques to analyse all kinds of signals from the brain. Another thing that I find very interesting, but I do not know how to measure that on a

continuous basis, would be in the area of bio-markers based on proteomics or anything like that.

**A. Bye:** I think one of the very simple things to get at is the messenger RNA. I think we costed out—it was about 20 cents an assay now and that you can use a Taqman system. I just wondered whether those sort of proteins are accessible enough in the plasma. When we considered it initially, within Glaxo Wellcome, it was like looking for a needle in a haystack; it was a very small amount, but in fact, the amplification systems that you can use, of course, you can see it so easily.

**M. Danhof:** I still would come back, and by thinking of a more mechanistic approach to really identify such markers also. If you just take them and just look at them and say "I do not know what sense to make out of them", rather than understanding the pharmacological system, what kind of a pattern would you expect? That would help you to select the most appropriate markers, which really reflects pharmacology. I also sincerely believe that pre-clinical pharmacology can help you to identify those markers, and use them throughout the development process.

**S. Jackson:** Have you had the opportunity of using these sorts of approaches to model pharmacodynamic drug interactions, where you have got two drugs with similar or even identical effects, to see how they behave in combination?

**M. Danhof:** That is one of the things that we are currently looking at. It is a very important issue waiting, first of all, if you have drugs which are converted into active metabolites. For example, we did some work on midazolam and alpha-hydroxymidazolam, where you really need receptor theory to predict what happens, so you cannot do it any longer on the basis of empirical interaction models. And also in designing rational combinations, if you look at psychiatry, for example, the dirtiest drugs seem to be the most effective; it is probably because they are benefiting from some interactions; if you would be able to identify them, then that would certainly help, and I would certainly think that by not taking those empirical models, the Hill equation, but using mechanism-based models, it allows you to characterize them in a more sophisticated and predictive manner than you do with the empirical models. I think there is a real opportunity there.

L. Sheiner: The question about multiple doses was an interesting point. The whole beauty of linear systems is that if you know what happens with one dose, you know what happens with all doses. Pharmacodynamic systems are generally non-linear, but if they are just saturable, and we have an idea of what that saturability looks like, then we are not too far from the economy of a linear system in the sense that we can simply quantify the non-linearity and have a fully predictive model: just use a wide-enough range of doses. But as soon as there is tolerance, or in general, a time-varying system, then the non-linearity can become quite complex. Engineers have long known that you can learn everything there is to know about an arbitrarily complex non-linear system if you observe its response to a so-called pseudo-random impulse input. That is to say, you have to give a (infinitely long) series of randomly spaced impulse inputs. I mention that because I think most drug developers would look askance at anyone who proposed a dosing design for a trial that randomised the time between doses across the people in the study. But that is exactly the kind of design that you need to understand a non-linear system! This is simply to say that everything Dr Danhof said has profound implications for design.

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**G.** Levy: And everything you said applies also to rebound effects, which are equally problematic.

**L. Sheiner:** Let me say what John Urquhart would say at this point: the experiment of nature, wherein patients take their drugs in many different patterns, presents a wonderful (and ethical) opportunity at the clinical level to find out about these highly non-linear systems as variable compliance may well imitate a pseudo-random input.

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