CHAPTER 8

Pharmacokinetic/ pharmacodynamic modelling in pre-clinical drug discovery

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8.1 *The importance of pharmacokinetic/pharmacodynamic modelling*

A concentration is only worth measuring if it produces an effect! The derivation of pharmacokinetic (PK) parameters from plasma concentration data and how these parameters relate to the disposition of the compound under study has been discussed earlier. However, PK studies serve little purpose if the compound is biologically inert. PK studies are performed because it is assumed that the parameters obtained are relevant to the *in vivo* activity of the compound. Perhaps the duration of action can be determined from the half-life? Perhaps the volume of distribution can be related to access to a receptor? In reality these relationships may not be straightforward. A short half-life does not necessarily equate to a short duration of action. A large volume of distribution does not ensure access to intracellular receptors. For PK parameters to be related to biological activity the relationship between the plasma concentrations (PK) and the effects (pharmacodynamics or PD) must be established through PK/PD modelling.

8.2 *Advantages of incorporating PK/PD modelling in the drug discovery process*

PK and metabolic screens are now an integral part of the drug discovery process. However, the interpretation of these screens is difficult if it is not known how the PK parameters in animals, along with *in vitro* metabolic stability data, relate to the required clinical activity in man. If the clinical target, in terms of PK and efficacy, is understood, the required pre-clinical properties of the molecule can be estimated by coupling PK/PD parameters and interspecies scaling. By performing these simulations to set the criteria for candidate selection, the chances of success in the clinic are enhanced. For example, within our own company a PK/PD study identified high protein binding as a problem in translating good *in vitro* potency of an inhibitor into good *in vivo* efficacy, and this information was then used to steer the lead optimisation process.

An understanding of the PK–PD relationship allows the importance of PK properties to be rationalised. In the drug discovery process, a project team may strive to achieve a molecule with a particular half-life, without knowing whether they must achieve that particular value or whether something rather shorter would do. PK/PD will enable this decision to be made, and this can potentially save months of unnecessary refinement of a molecular series. For example, the duration of action of an irreversible neutrophil inhibitor was shown to be governed by the turnover of neutrophils and was not related to the half-life of the inhibitor.

Understanding the sensitivity of PD to changes in PK can also clarify the relevance of potential drug–drug interactions. A PK interaction need not be a problem if it has an insignificant effect on PD. Likewise, disease and ageing may affect PK, but this may not necessarily translate to an affect on PD. It must always be remembered that PK is a surrogate for PD and not a goal in its own right.

The slope of the PD concentration response curve can have a significant impact on the suitability of a compound class to its disease target. A steep response curve will give a rapid onset and termination of activity, a desirable property of an anaesthetic perhaps. It will also make the PD very sensitive to small changes in PK. A shallow response curve would be more suited to diseases, such as high blood pressure, where safe chronic dosing is required.

The PK–PD relationship may not be an obvious one. There may be a delay between the PK profile and the effect, such as is seen for the effects of corticosteroids on cortisol levels. However, such relationships can usually be modelled, and the relevance of PK understood. Furthermore, if the relationship between plasma concentrations and centrally mediated effects of a drug can be modelled we can obviate the need, during drug development, for measuring levels of compound in the brains of animals or the cerebrospinal fluid in man.

Many of our receptor targets mediate more than one physiological function. For example, the adenosine A1 receptor controls cardiovascular, metabolic and central

nervous system (CNS) functions. Understanding the *in vivo* PK–PD relationship for all of these processes allows us to optimise a molecule to a particular physiological target.

Finally PK/PD has a unifying effect on the scientific disciplines with the drug discovery process. Pharmacokineticists need to work closely with both *in vivo* and *in vitro* pharmacologists, and with clinical pharmacologists to provide the link between pre-clinical and clinical efficacy.

8.3 *PK/PD in the drug discovery process*

8.3.1 The changing role of DMPK in drug discovery

When drug metabolism and pharmacokinetics (DMPK) was first recognised as a key discipline within the pharmaceutical industry, its function was reserved for the development process. The driving force was from the regulatory bodies who recognised the need to understand the disposition of drug molecules in order to understand and interpret safety and efficacy studies (both animal and clinical). Soon after, many companies recognised that understanding more about drug disposition prior to the development phase was advantageous to the process. However, the bioanalytical tools available at the time (e.g. HPLC/UV) meant that disposition studies could only be performed on a limited number of compounds due to the time taken in methods development. Consequently DMPK studies usually took place on a limited number of compounds prior to full development. As the data was generated so late in the discovery process, any shortcomings in the disposition of a molecule could not be fixed as the chemical programme had focussed for a long time on one chemical series. The widespread use of LC/MS has changed the situation radically. Sensitive and specific assays can now be developed rapidly, and providing DMPK support to the discovery process at the earliest stages of lead optimisation is a reality. The consequence of this is that decisions on entire discovery programmes can now be made based on DMPK criteria. For that reason it is imperative that those scientists supplying that support can fully interpret the meaning and relevance of their data. As stated in the introduction, PK alone is not a reliable indicator of a compound's suitability for the market place. To make the right decisions, the link between PK and PD must be understood.

8.3.2 PK/PD in a research strategy

A typical way in which PK/PD can be incorporated into the research process is outlined below. It is very important to recognise that the purpose of this strategy is to make the right decisions and reduce the risk of taking an inappropriate molecule

through to the expensive process of drug development. Usually the PK/PD models will be far from perfect, and the study design may not be ideal. The understanding of the biological processes involved in the PD response may be far from clear. It is therefore important to take a pragmatic approach to PK/PD, using the simplest of models and a study design commensurate with making the right decision. Remember always that forecasting what will happen in patients (the ultimate goal) is an imprecise science not only from the point of view of PK and PD, but also in selecting the appropriate pre-clinical disease models.

8.3.3 Defining the PK target

Many companies are now using *in vitro* metabolic screens at an early stage of the selection process. Traditionally compounds with high turnover are rejected in favour of metabolically stable molecules. An understanding of the PK–PD relationship will enable a reasoned judgement on compound selection/rejection to be made. Lack of stability may not necessarily be a problem. Likewise, the relevance of *in vitro* permeability screens, such as MDCK cell monolayers, is clearer if the physiological location of the target receptor is known. Both of these concepts combine *in vivo* to determine clearance, volume and half-life. In addition, the requirement for good oral bioavailability is not always given. A compound acting on the gastrointestinal (GI) tract may work either topically or systemically, and it is important to understand which applies to a given compound class. Conducting PK/PD studies on representative molecules from a given compound series at an early stage of the discovery process enables these issues to be resolved, and hence the screens can be interpreted correctly. At the same time a greater understanding of the PD model is obtained.

Once the relevance of PK parameters has been established from the PK/PD studies, the hypothesis should be regularly tested to ensure continued validity. PK/PD studies using molecules with widely differing properties (clearance, volume, physicochemistry) maintain confidence in the model.

Throughout the pre-clinical discovery process the assumption is made that data has some relevance to patients, and invariably an animal model is utilised at some stage. Traditionally, PK in man has been forecast from pre-clinical data using allometric scaling of the PK parameters. The addition of PK/PD to the project knowledge base enables this to be taken one step further. If the PK–PD relationship in animals has been defined, along with *in vitro* comparative data on the receptor binding in animals and man, it is possible to forecast not only the PK but also the magnitude and duration of pharmacological effect in man. Throughout this process it is assumed that the forecasts to man have some chance of success. As with all extrapolations, these forecasts must be viewed with caution, recognising the assumptions made on the way. None-the-less, forecasting based on PK/PD

knowledge provides the best chance of selecting the most appropriate molecule for progression into the clinic.

8.3.4 PK/PD IN PRE-CLINICAL DRUG DEVELOPMENT

In its broadest sense, PK/PD has for many years been an integral part of the pre-clinical package in the form of toxicokinetics (see toxicokinetics chapter). Parameters of exposure such as AUC and C_{max} are related to general toxicological findings. This chapter will, however, focus on PK/PD relating to specific pharmacological events. The utility in the discipline of safety pharmacology is obvious. If the relationship between plasma concentrations and both wanted and unwanted effects can be modelled, a very clear understanding of the potential acute therapeutic window in man can be obtained. The dosage regime can be optimised to maximise safety. In addition, comparative studies with several compounds of the class can aid in selecting the safest. However, getting PK/PD data that can be used in this way presents significant practical difficulties. Not the least is the fact that taking sufficient blood samples routinely from animals involved in cardiovascular or behavioural studies may impact on the very pharmacological events that are under study. For this reason anything other than the simplest of PK/PD models may not be practical.

8.4 *Principles of PK/PD modelling*

8.4.1 DATA REQUIREMENTS

Both plasma concentration and effect data versus time are required. The PK data should preferably be in the form of a compartmental model, although non-compartmental analysis may be adequate. Importantly the time points may need to be different for the PK and PD measurements. The drug concentration samples should be taken to fully characterise the PK profile. The effect measurements should be taken at times that characterise the full range of the PD response. Ideally, all should be done simultaneously in the same animal. However, this is often impractical for a number of reasons:

1 The dose that produces the desired PD response may give plasma concentrations that cannot be detected. In this case a higher dose should be given for the PK determination, and linearity of PK assumed.
2 Taking blood samples may affect the response.
3 Insufficient samples for drug analysis can be taken from the animal in the PD model. Under these circumstances separate PK studies should be

carried out, taking into account route, formulation, species, strain and anaesthetic state.

8.4.2 The sigmoid E_{max} model

For most purposes the most complex PD model required in drug discovery is the sigmoid E_{max} model. In this, plasma concentrations are related to effect by the following equation:

$$\text{Effect} = \frac{E_{max} \times C^N}{EC_{50}{}^N + C^N} + E_0$$

This represents the following relationship between effect and concentration and is illustrated in Figure 8.1.

E_{max} is the maximum effect that can be produced by the drug, at infinite concentration (all receptor-mediated responses have a maximum!).
EC_{50} is the concentration of drug that produces 50 per cent of the maximum effect. E_0 is the effect produced in the absence of drug (placebo or baseline noise). N is the slope of the response curve. A large value of N (e.g. >1) gives a rapid transition from minimum to maximum effect with concentration. The converse is true for a small value of N (e.g. <1).

Between 20 and 80 per cent maximum response, the effect is approximately proportional to log concentration. This will be of no surprise to pharmacologists, who have been doing two-point log dose response curves within the 20–80 per cent range for many years.

If the *in vivo* PD response curve can be defined, the effect versus time profile can be modelled for various PK scenarios, and appropriate decisions made. For a

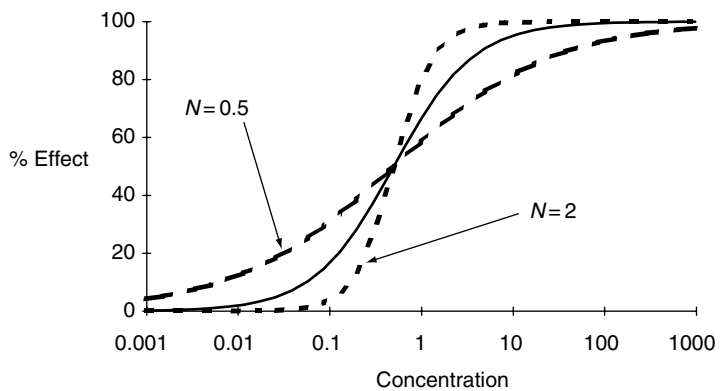

Figure 8.1 *Sigmoid E_{max} model.*

detailed review of PK/PD modelling, with examples of the use of WinNonlin™ the reader is referred to Gabrielsson and Weiner (1997).

8.4.3 Delayed response

Very often a simple plot of effect versus concentration, as shown above, does not yield a graph that can be used predictively. This may be because there is a delay between the concentration and the effect as shown in Figure 8.2.

This situation is often referred to as counter-clockwise hysteresis. The arrow on the graph indicates the third dimension of time. Clearly there is not a single solution to this concentration–effect relationship, as the same effect is produced by widely differing concentrations depending on whether the measurements are taken sooner or later after drug administration. The situation can be further visualised as shown in Figure 8.3. In this example the EC_{50} could be either 75 ng/ml or 15 ng/ml depending on when it was measured.

Currently two methods are available in WinNonlin™ for modelling the sigmoidal PD relationship to plasma concentrations when the response is delayed relative to the plasma concentrations. These models can then be used predictively.

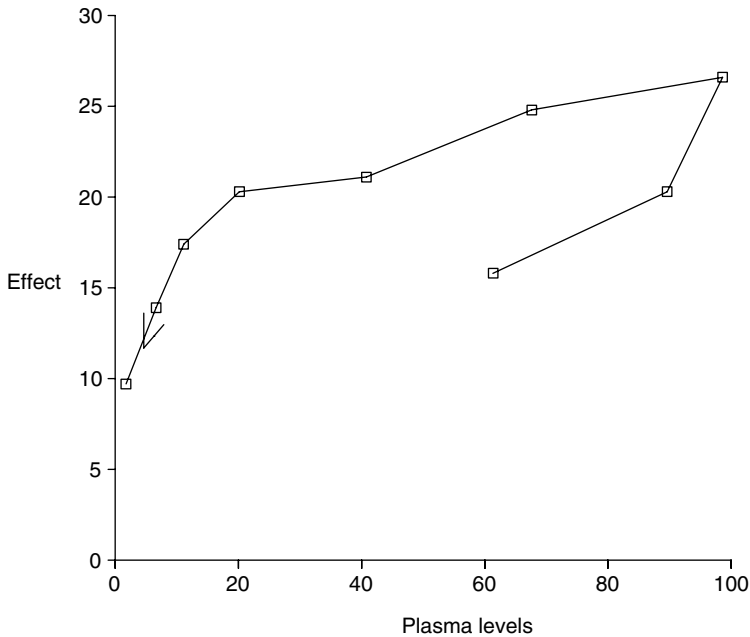

Figure 8.2 *Plot of effect versus plasma concentration showing counter-clockwise hysteresis.*

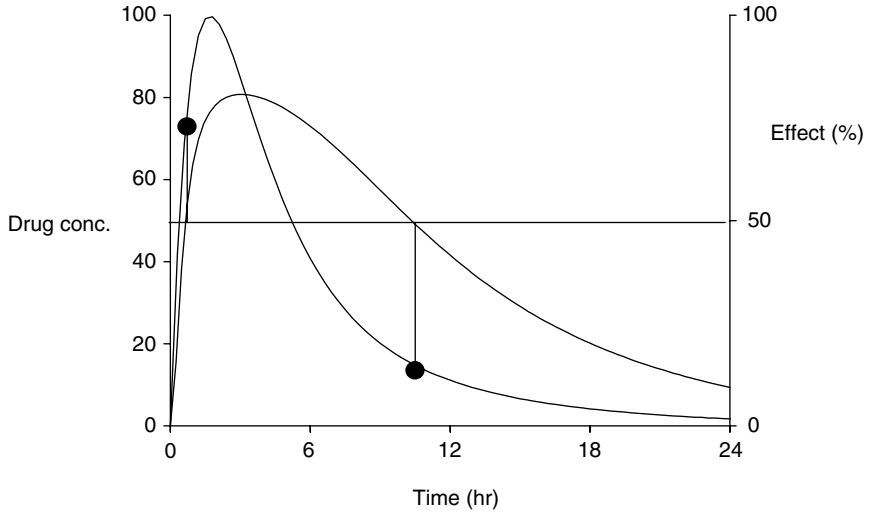

FIGURE 8.3 *Plot of concentration and effect versus time showing the effect lagging behind the plasma concentrations.*

The link model (Holford and Sheiner, 1982) assumes that the delay can be explained by the target receptor being in a separate, non-plasma compartment. Unlike normal PK compartments, this has no volume and hence does not contribute to the mass balance. A first order rate constant, *Keo*, describes the rate of equilibration of this compartment with plasma, and allows a PK/PD model to be constructed that can be used predictively.

The second model is the indirect response model (Jusko, 1990). It assumes that the delay is biochemical. In simple terms, it assumes that the biochemical function under investigation is in a state of equilibrium, with a zero order process producing the function, and a first order process destroying it. A drug can either stimulate or inhibit the production of the function, or stimulate or inhibit the destruction. This is analogous to the steady state infusion situation in PK, where a change in either infusion rate or elimination will change the steady state plasma concentration. As with the link model, the indirect response model can be used predictively with data that shows a delay between plasma concentration and response.

8.4.4 IMPACT OF PK AND PD PARAMETERS ON *IN VIVO* POTENCY AND DURATION

PK/PD models enable the magnitude and duration of response to be predicted under various scenarios. Whilst the half-life alone does not necessarily reflect the duration of action (the latter is determined by the Hill coefficient, hysteresis and EC_{50} in addition to the half-life), some general rules can be formulated to predict the effect of changing

TABLE 8.1 *Impact of half-life on duration of effect*

Half-life (hours)	Time above 50% effect (hours)
0.5	3
1	6
2	9
4	17
8	30

$E_{max} = 100$, $E_o = 0$, $EC_{50} = 20$, $N = 1$, $Keo = 0.9$, $Co = 270$.

TABLE 8.2 *Impact of dose on duration of effect*

	Time above 50% effect (hours)	
Half-life (hours)	**10 mg/kg**	**20 mg/kg**
0.5	3	4
2	9	11

$E_{max} = 100$, $E_o = 0$, $EC_{50} = 20$, $N = 1$, $Keo = 0.9$, $Co = 270$.

half-life, dose and potency on duration. Table 8.1 is an example of a series of compounds with identical PD properties but differing half-lives. This illustrates the point that in general, doubling the half-life doubles the duration of effect.

The effect of doubling the dose (or doubling the potency) is not so dramatic (Table 8.2). That is, in general doubling the dose increases the duration of action by only one half-life. Thus increasing the half-life is a much more efficient means of enhancing the duration of action than is increasing the dose or potency.

8.5 *Summary*

The conventional use of PK only provides information about the disposition of the drug molecule. By joining forces with the pharmacologists the pharmacokineticist can develop PK/PD models that can describe the relationship between plasma concentration and effect. This knowledge allows the likely effect versus time profile in man to be forecast from animal data. It also enables the impact of changing PK parameters on the PD profile to be evaluated. Perhaps most important of all, it assists drug discovery scientists in setting the appropriate PK target during drug candidate selection so that the chance of clinical failure due to inappropriate PK and PD is minimised.

8.6 *References*

Gabrielsson, J. and Weiner, D. (1997) *Pharmacokinetic and Pharmacodynamic Data Analysis*, 2nd edition. Apotekarsocieteten, Stockholm.

Holford, N.H.G. and Sheiner, L. (1982) *Pharmacol. Ther*. **16**, p. 143.

Jusko, W.J. (1990) *J. Clin. Pharmacol*. **30**, p. 303.

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