13

Quantitative Pharmacological Relationships

13.1 Introduction

As stated in Chapter 1, it is quite common to read that there are two branches of pharmacology: pharmacodynamics and pharmacokinetics. At a more specific level, many authors prefer to distinguish between the description of overt effects of drugs and mechanistic studies (as subdivisions of pharmacology), limiting the use of the word pharmacodynamics to studies of the relationship between drug concentrations, and mechanisms, at sites of action. This chapter and the one that follows it are concerned with the relationship between drug concentrations in body fluids, principally plasma, and the intensity and duration of drug effects, sometimes called 'dose–response and time–action relationships'.

It is generally accepted that the effects of drugs are usually greater when exposure is greater, and that the effects of drugs that are rapidly removed from the body disappear quickly. Conversely, reduced exposure is thought to reduce effect, either by reduction in dose, or by use of a drug that is rapidly removed from the body. However, when these relationships are studied in detail relatively complex relationships are observed. During the last twenty-five years there has been explosive growth in our understanding of what has come to be known as the pharmacokinetic/pharmacodynamic (PK/PD) relationship. PK/PD modelling uses measurements of overt effects, and of drug concentrations in plasma and at other sites, to explore mechanisms. This is conveniently studied through:

- Fundamentals of dose–effect relationships (dose–response curves, recorded principally *in vitro*).
- Study of similarities and differences between *in vitro* and *in vivo* data.
- Consideration of the potential for variation.
- Specific examples of dose–effect and concentration–effect relationships *in vivo*.
- PK/PD modelling, which integrates pharmacokinetic concepts with concentration–effect relationships.
- Concepts of loading and maintenance doses for long-term treatment.

13.2 Concentration–effect relationships (dose–response curves)

Dose–effect relationships follow from the nature of the reversible interaction between a drug and its receptor. A drug may be an agonist and exert a stimulatory effect on the receptor, or it may be an antagonist and act by binding to the receptor to prevent the effects of an agonist (Section 1.1).

The effects of a drug do not increase indefinitely with increasing doses, as there is a finite number of receptors. The reversible binding of a drug, D, to its receptor, R, can be assessed by the Law of Mass Action:

$$D + R \rightleftharpoons DR$$

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where DR is the drug–receptor complex. The equilibrium constant (Section 1.5.1), K_D, is related to the molar concentrations of the species at equilibrium:

$$K_D = \frac{[D][R]}{[DR]} \tag{13.1}$$

The total concentration of receptors is the sum of the bound and non-bound receptors, $[DR] + [R]$, and the proportion, or fraction, of receptors bound, f_A, can be obtained by rearrangement of Equation 13.1:

$$f_A = \frac{[DR]}{[DR] + [R]} = \frac{[D]}{[D] + K_D} \tag{13.2}$$

This is the equation of a rectangular hyperbola [Figure 13.1(a)].

K_D has units of concentration and is numerically equal to the concentration at which 50% of the receptors are occupied. The lower the value of K_D the greater is the *affinity* (i.e. the tendency to bind) of the agonist for its receptor.

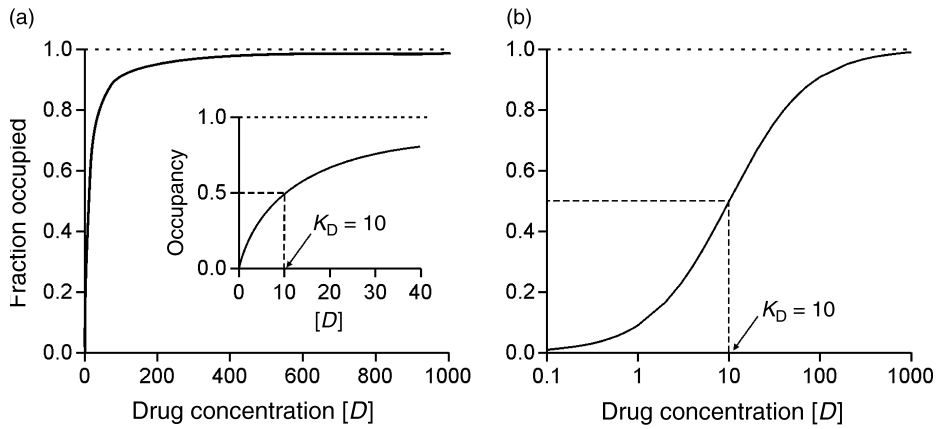

Figure 13.1 (a) Fraction of receptors occupied (occupancy) as a function of drug concentration. K_D is numerically equal to the concentration at which half the receptors are occupied (Inset). (b) Logarithmic transformation converts the hyperbola into a symmetrical sigmoid shape typical of log(dose)–response curves.

The measured response to a drug is related, but not necessarily directly proportional to receptor occupancy. Agonists that interact with their receptors to produce the maximum response possible are referred to as 'full' agonists whereas agonists that are incapable of producing the maximum response, even when all the receptors are occupied, are referred to as *partial agonists* (Figure 13.2). A partial agonist in the presence a full agonist may antagonize the effects of the latter and so partial agonists are sometimes called *agonist-antagonists*.

Figure 13.2 illustrates some important features of agonists and log(concentration)–response curves. First, it is usual to plot the response as the percentage of the maximum that a full agonist can produce. If the responses are from an *in vitro* experiment using isolated tissues, say guinea pig ileum, then different pieces of tissue will give different responses, but normalizing the results to the maximum obtainable with each tissue allows comparison between experiments and average responses can be plotted. Such dose–response curves, where the response is continuously variable between the minimum and maximum response are 'graded' response curves. For *in vivo* data 'quantal' response curves may be used. With these, some measurable

endpoint is defined, for example pain relief, and then the numbers of subjects from a test population that attain the endpoint are recorded for each concentration or dose of drug. The *y*-axis of Figure 13.2 for a quantal dose–response curve would be 'percentage of subjects responding', the maximum (100%) being when all the subjects responded to the treatment.

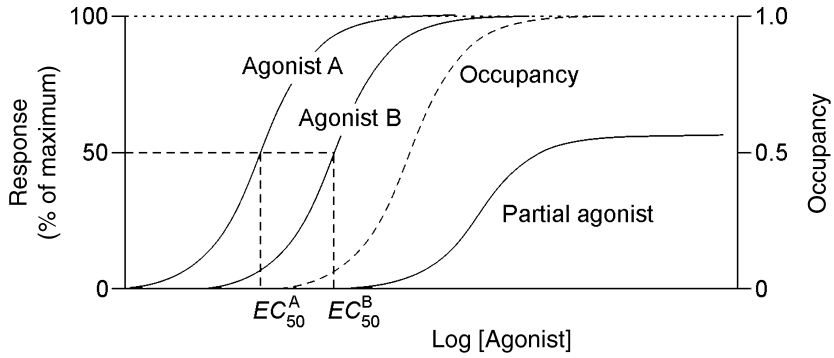

Figure 13.2 Log(agonist concentration)–response curves. Agonist A is more potent than B because it has a lower EC_{50}. The partial agonist cannot elicit the maximum response even when all the receptors are occupied.

In Figure 13.2, the curves for agonists A and B have been positioned to the left of the occupancy curve illustrating that not all the receptors have to be occupied for the response to be maximal. Stephenson (1956) introduced the term *efficacy* to describe the way in which agonists vary in the response they produce, even when they occupy the same number of receptors. The partial agonist is less efficacious than the full agonists because it cannot elicit as great a response. The full agonists are considered equi-efficacious as they both have maximal efficacy. The responses to agonist A occur at lower concentrations than those for agonist B. Agonist A is more *potent* than agonist B, that is less drug is required to obtain a defined effect. Potency is usually assessed from the concentration producing 50% of the maximum response, EC_{50}. For a quantal response, EC_{50} or ED_{50}, is the dose at which 50% of the *test* population respond. It may seem paradoxical, but partial agonists can be highly potent. This is true of the opiate agonist, buprenorphine, which has high affinity for the μ-opioid receptor. As a consequence, it can displace other opiate analgesics such as morphine, reducing the pain relief and possibly causing withdrawal symptoms in addicts.

A further consideration is that the slopes of dose–response curves may differ. Some drugs have steep curves whilst others have shallow curves. The response at any concentration, C, can be written in terms of the maximum response, E_{max} and EC_{50}:

$$\text{response} = \frac{E_{max} C^{\gamma}}{EC_{50}^{\gamma} + C^{\gamma}} \tag{13.3}$$

where γ is a factor that defines the slope, or shape, of the concentration–effect curve. Pharmacodynamic models that use Equation 13.3 are referred to as E_{max} models. When γ is large the slope of the curve is steep and the effect may appear to be almost all or nothing because the response may go from the minimal to the maximum effect over a very small range of concentrations.

13.2.1 Antagonism

Antagonists have affinity for receptors but not efficacy. Consequently, their effects can only be assessed in the presence of a suitable agonist. Antagonists can be competitive, that is they compete with the agonist for

receptor binding sites, or non-competitive, these often bind covalently to the receptor. Competitive antagonism is reversible because the antagonist can be displaced by increasing the concentration of agonist, and, provided sufficient agonist is used the maximal tissue response can be obtained. This results in log(agonist concentration)–response plots constructed in the presence of differing concentrations of antagonist being parallel [Figure 13.3(a)].

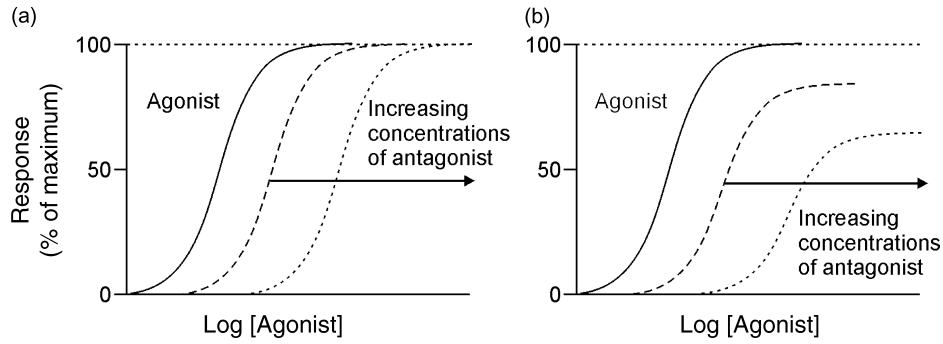

Figure 13.3 (a) Competitive antagonists cause a parallel shit in log(agonist concentration)–response curve to the right. (b) Non-competitive antagonists move the agonist curve to the right with a decreasing maximum response, leading to a non-parallel shift.

A non-competitive antagonist reduces the maximum tissue response. In effect, the numbers of viable receptors are progressively reduced with increasing concentrations of non-competitive antagonist so the maximum response declines. This leads to a non-parallel shift of the log(antagonist concentration)–response curve [Figure 13.3(b)].

The potency of antagonists can be assessed from curves of the type shown in Figure 13.3. Dose–response (*DR*) or concentration–response (*CR*) ratios are calculated:

$$CR = \frac{EC_{50} \text{ of agonist in presence of antagonist}}{EC_{50} \text{ of agonist alone}} \tag{13.4}$$

for a range of antagonist concentrations. The more potent an antagonist the greater will be the value of *CR* for a given molar concentration of drug. The potencies of competitive antagonists are compared using the pA_2 values, where pA_2 is the negative logarithm of the molar concentration of antagonist when $CR = 2$. The notation is analogous to that used for pH, the p indicating a negative logarithm.

13.2.2 Variation

As stated, much of the foregoing referred to *in vitro* experiments, in which isolated tissue samples are exposed to fixed concentrations of drugs, and tissue responses are measured, as contractions of the tissue, release of biochemicals, chemical change of exogenous substrates, etc. In these experiments, variations in response occur to fixed concentrations, or a range of concentrations can induce a defined response. For any drug–effect combination, there will be a mean response to a fixed dose. Responses will be seen on either side of this mean and there will be a range of response. The distribution of responses can be assessed mathematically. The commonest distribution is the symmetrical 'normal' distribution. This involves the largest proportion of the responses being closest to the mean, with successively smaller proportions of the responses being at

successively larger intervals from the mean. The usual measure of scatter in the normal distribution is the standard deviation, σ,

$$\sigma = \sqrt{\frac{\sum(x-\bar{x})}{n-1}} \tag{13.5}$$

which is the square root of the variance. The variance (σ^2) is obtained by summing the squares of the deviations of each result, x, from the mean result $\bar{x}$ and dividing by one less than the number (n) of observations ($n-1$), called the 'degrees of freedom':

$$\sigma^2 = \frac{\sum(x-\bar{x})}{n-1} \tag{13.6}$$

A large standard deviation indicates a wide scatter of results with a wide distribution curve. The number of degrees of freedom is equal to the number of data points that must be used to calculate the standard deviation. It is $n-1$ because the last deviation can be deduced from the fact that $\Sigma(x-\bar{x}) = 0$. For a normal distribution approximately 68% of the measurements lie within $\pm 1\sigma$ of the mean, ~95% are within $\pm 2\sigma$ and ~99.7% are within $\pm 3\sigma$ of the mean. Data should be tested for 'normality' before any parametric statistical tests are performed as otherwise the appropriate tests are non-parametric ones. Figure 13.4 shows that salicylate concentrations at 3 h in 100 subjects were normally distributed.

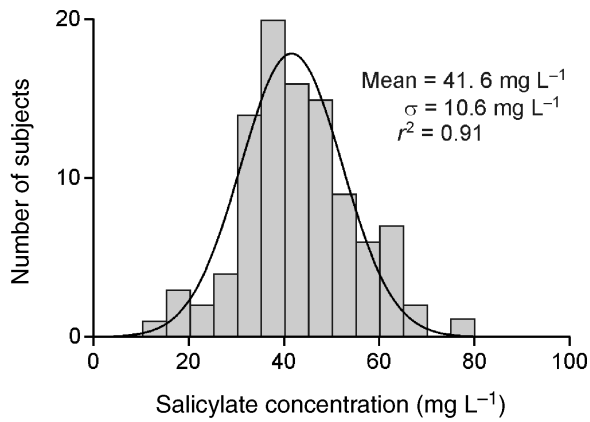

Figure 13.4 Serum salicylate concentrations in 100 subjects 3 h after 35 mg kg^{-1} sodium salicylate orally. Data were fitted to a normal distribution (solid line).

It should be noted that while the normal distribution is common in pharmacology, other distributions occur frequently. The commonest variation is skewing, with one side of the curve tailing much further from the mean than is the case with the other side. Bimodal distributions also occur. If skewed data can be transformed so that the results are normally distributed then parametric statistics can be applied to the transformed data. For example if the logarithms of the observations are normally distributed, then the statistics are performed on the logarithms of the observations.

One particular aspect of the distribution of pharmacological phenomena relates to whether responses *in vivo* are normally distributed with respect to dose or log(dose). The basic work was done with log (dose)–effect curves, for graded responses. When the response is measured as percent of the biological units affected, a so-called quantal response, the log(dose)–effect curve is an integrated frequency distribution diagram based on a log(dose). Thus original work implies that pharmacological responses are log normally distributed. However, *in vivo*, the exposure range is smaller, especially in human pharmacology, and data may

appear to be normally distributed with respect to dose. Data collected in humans is sparse, consisting mainly of plasma concentration data, such as the salicylate data in Figure 13.4, which is not, strictly speaking, response data. These data, generally speaking, appear to indicate normal distribution with respect to dose in some cases and log(dose) in others. However, the data of Figure 13.5 are instructive. This figure shows the warfarin dose in a group of patients who achieved a prothrombin ratio of 1.7.

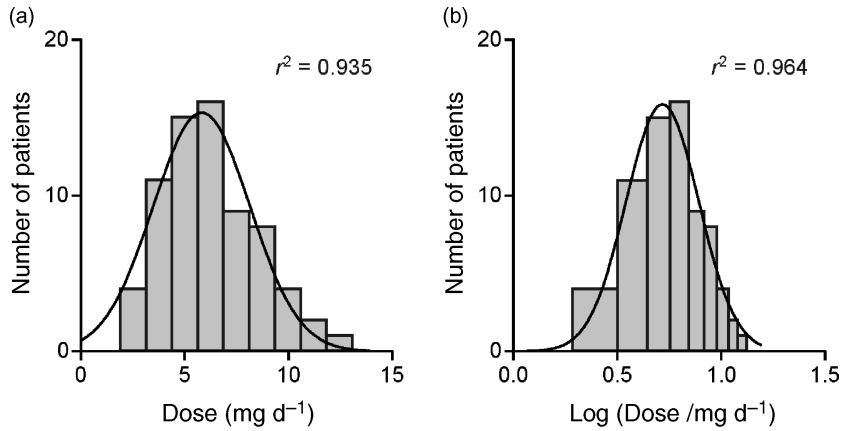

Figure 13.5 Warfarin dose (mg/day) to achieve a prothrombin ratio of 1.7 (INR = 3.4). (After White *et al.*, 1987, 1991).

Distributions are shown for warfarin response as number of patients in each dose category (thus relating incidence of effect to a range of fixed doses – a quantal response) related to dose, and also to log(dose). The statistics show a better fit to a log–normal distribution. It is often not easy in such circumstances to determine whether the distribution is normal or log–normal, principally because, as stated earlier, of the narrow range over which responses are commonly recorded in human studies. Similar results have been reported with suxamethonium.

13.2.3 Some illustrations of dose–response curves in vivo

Although it is not difficult to demonstrate a 'perfect' dose–response curve *in vitro*, demonstration of such perfect relationships in many other situations is much more difficult. Some examples are illustrated below.

- *In vivo*, the log(dose)–response curve may be a straight line from a restricted part of the available range. For example, in Figure 13.6, for sleeping times for phenobarbital in mice, the upper limit is fixed by a different drug response in that higher doses cause death. The lower limit is the recording of sedation rather than sleep.
- In human pharmacology it is often necessary to work at the lower end of the dose–response curve because of the prime importance of the safety and comfort of the subjects involved (Figure 13.7).
- In chemotherapy it is usual to work at the upper end of the curve, as antimicrobial drugs usually have a wide margin of safety and the maximum effect against the microbes is required (Chapter 14).
- In psychopharmacology it is commonly impossible to define or achieve the maximum possible effect, so the upper limit is less than 100% in a quantal curve. Additionally, there is a large subjective contribution (placebo effect) and some response is obtainable from a placebo preparation, so the graph does not necessarily go through the origin (Figure 13.8).
- Compensatory reflexes play a considerable part in modifying dose–response curves when the measurable effect is a change in blood pressure; this makes the observations highly time dependent (Section 14.2.2).

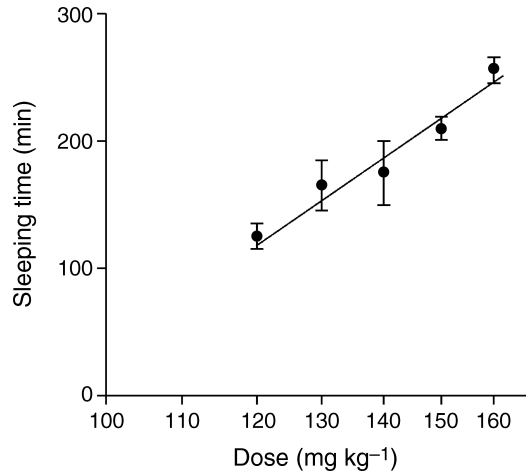

Figure 13.6 Dose–response relationship for phenobarbital concentrations (logarithmic scale) and sleeping time in mice. Each point is the mean of six to eight mice ± SEM. Below 120 mg kg^{-1} the drug had only a sedative effect. Above 160 mg kg^{-1}, some of the mice died.

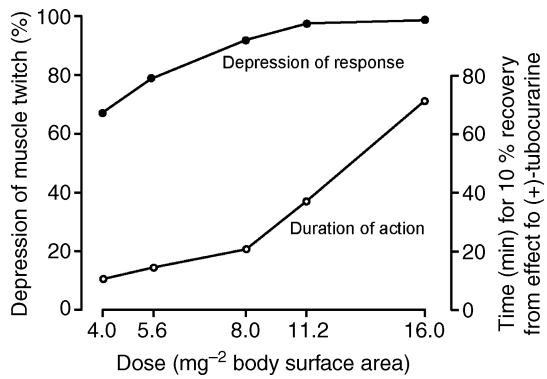

Figure 13.7 Dose–response curves for depression of standard muscle twitch response and for duration of action (time required for 10% of standard response to return) in human subjects given (+)-tubocurarine ($n \geq 20$ at each time point). (Redrawn from Walts & Dillon, 1968.)

- Latent pharmacological effects can show unusual dose–response relationships. For example, the effect of warfarin on clotting time occurs after a considerable delay and after the peak plasma level of the drug has passed. In such a situation, the perfect dose–response relationship is obscured (Chapter 14).
- In teratology, there is a dose range which leads to live births of malformed fetuses (Figure 13.9). There is a higher dose range that causes foetal death illustrated in ferrets by resorption, with no live births. Thus, while a dose–response curve for resorption is not particularly unusual, the dose–response curve for abnormal survivors has a peak, with a fall-off with both higher and lower doses.
- Preventive treatment with drugs is common in therapeutics. A relationship between degree of prevention (which desirably is 100%) and dose is very difficult to demonstrate, especially as many diseases requiring preventative treatment, notably mania and epilepsy, are episodic in their occurrence (Chapter 14).

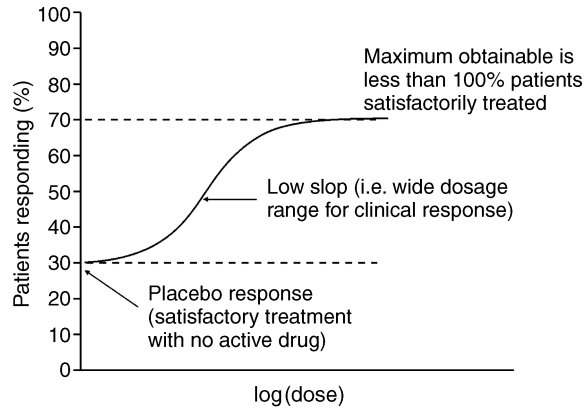

Figure 13.8 Model quantal dose–response curve for psychopharmacology.

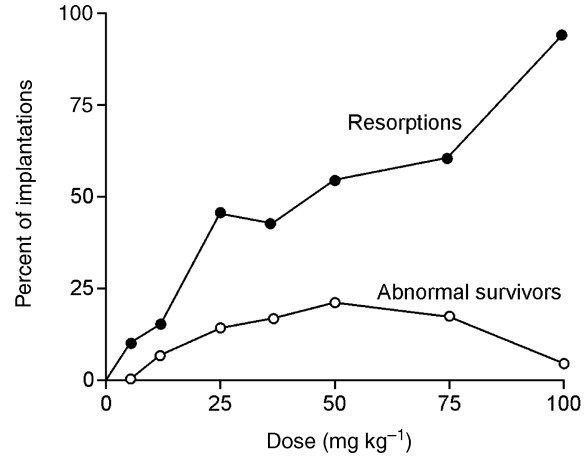

Figure 13.9 Dose–response curves for the teratogenic activity of trypan blue in ferrets. Foetuses that do not survive the pregnancy are reabsorbed (resorptions). The proportion of live abnormal foetuses declines as the dose increases. (Redrawn from Beck & Lloyd, 1964.)

13.3 The importance of relating dose–effect and time-action studies

Historically, while drug effects were related almost exclusively to dose, both *in vitro* and *in vivo*, by pharmacologists, the possibility that *time since dose* is important was known to the ancients from their experiences with alcohol and other naturally occurring pharmacological agents, and was even documented by Shakespeare in his play *Romeo and Juliet* (in which Friar Lawrence gave Juliet a drug designed to induce a death-like coma lasting exactly 42 hours, only to have Romeo turn up too early, misunderstand the situation, and commit suicide in grief just as Juliet was waking up). However, the recognition by scientists that time since dose is important in quantitative pharmacology is more recent. This fact was introduced in Chapter 4. It is clearly the basis for wear-off of effect, but, additionally, it actually changes the *relationship between effect*

and concentration in plasma, and this has been known for a relatively short time. Pioneering work had been done by Levy and Nelson, and Wagner, in particular, in the 1960s on single dose-plasma level-effect relationships and on the duration of action of drugs as a function of dose (Levy, 1964a and b, and 1965; Levy and Nelson, 1965; Wagner, 1968a and b). At about the same time, Brodie and colleagues demonstrated how complicated the relationships are when drugs with multi-compartment distribution are studied in this context (e.g. Brodie, 1967). Earlier, Murphy and Lasagna (1961) using diuretics, had found that depending on whether a cumulative effect (24-h urine production) or an 'instant' effect (rate of urine flow at a particular time) was measured, different relationships of response were possible. Also in the 1960s, Levy and Nagashima (Levy and Nagashima 1969; Nagashima and Levy 1969) demonstrated the relative time courses of anticoagulant concentration and effect.

Thus, the relationship between effect and concentration of drug in plasma should not be expected to be constant or simple, and it can vary with time. More recently, the emphasis has been on combined modelling of effects and concentrations. As stated, the broadly-accepted dose–effect relationships of pharmacology were largely elucidated by *in vitro* experimentation, with organ bath drug concentrations as the reference point. The salicylate example in Figure 13.4 introduced, for our purposes, the concentration in plasma as the reference point for *in vivo* work. Time–action considerations require the presumption of a certain relationship between the concentrations of drugs in the fluids in the vicinity of the drug receptors *in vivo* and concentrations in plasma *in vivo*. Logic requires the following assumptions:

- Drug concentrations in the fluids in the vicinity of drug receptors *in vivo* and *in vitro* are analogous.
- The concentrations of drug–receptor complexes are a function of the concentration of drug molecules in the fluid in the vicinity of the receptors.
- Drug distribution through body fluids occurs by reversible diffusion and by binding processes.
- Drug concentrations in plasma water *in vivo* are analogous to the concentrations in the *in vitro* experiment; the distinction between plasma water and whole plasma should be particularly noted.

13.3.1 The fundamental single dose time-action relationship

With *in vitro* experimentation, the drug is added and removed by the experimenter, and the concentration changes little if at all between addition and removal. *In vivo*, the concentration of the drug in whole plasma and plasma water rises and falls with time, as shown in earlier chapters. *In vivo*, quantitative relationships between effect and drug concentrations are superimposed upon a changing drug concentration. The model presented as Figure 4.1, is the model for the relationship between effect and concentration for an oral or other non-intravenous dose. This model makes no presumptions regarding linearity of kinetics or response relationships. However, in some of the earliest studies of the relationship between concentration and effect, Gerhard Levy made two fundamental deductions:

- If the effect is measured in the middle of portion of an *in vivo* log dose–response relationship, and if the decline of plasma concentration is by first-order kinetics, then the effect wears off at a constant rate.
- If the same assumptions apply as in the previous bullet, doubling of the dose extends the duration of effect by one half-life.

However, the above only applies to a bolus intravenous injection and assuming a single compartment model applies. Even for a simple single compartment model, the duration of action will not necessary double for a doubling of an oral dose. The change in duration is dependant on where the minimum effective concentration is relative to $C_{max.}$ (Figure 13.10).

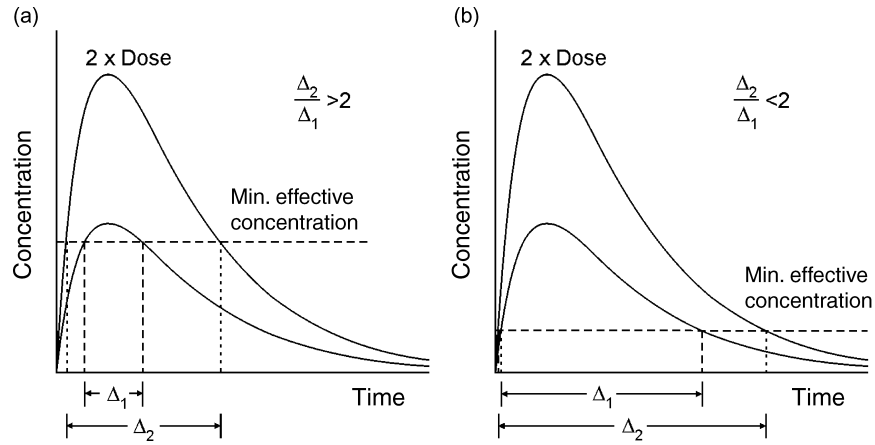

Figure 13.10 The proportionate change in the duration of effect (Δ) on doubling the dose depends on where the minimum effective concentration line is initially. (a) When the line is close to the maximum concentration, doubling the dose more than doubles the duration. (b) When the line is much lower, doubling the dose may have little effect on the duration of action.

Thus, when the simplest models for oral doses apply, an increase in dose causes a proportional increase in C_{max}, no difference in t_{max}, and a variable increase in duration of effect. Within this limitation, if the effect were proportional to dose, a doubling of dose would lead to a doubling of effect, and a less than doubling of duration of effect. Careful consideration of the dose–response relationships discussed earlier leads to the inevitable conclusion that the foregoing is a special case that is unlikely to occur. Thus, if the dose and concentrations are in the upper part of the dose–response curve then doubling of the dose and concentration will cause less than a doubling of effect. Conversely, if the dose and concentrations are in the lower part of the dose–response curve, then doubling of the dose and concentration will lead to more than a doubling of effect. Similarly, if the absorption of the drug is saturable, then there will also be less than the expected increase in effect when the dose is increased. By the same standard, a saturable first-pass effect can cause more than the expected increase in effect, unless the first-pass effect produces a metabolite through which the drug exerts its effect, then the opposite will occur. If metabolism is non-linear (e.g. phenytoin), then an increase in dose will cause more than the expected increase in duration of effect; there will also be more than the expected increase in C_{max}, and therefore in maximum effect, but worse still, a larger dose will have a later t_{max}. If metabolism occurs with zero-order kinetics (e.g. alcohol), then the duration of effect will be doubled if the dose is doubled, if all other simpler rules apply. If the drug shows saturation of protein binding in the therapeutic range, then doubling of the plasma concentration will cause more than a doubling of the concentration in plasma water, and more than a proportionate increase in effect, unless, of course, the receptors are saturated! If the drug exhibits two-compartment distribution there may be an even more complex relationship between dose, concentration and effect at any particular time, and, in all cases, the patterns shown during long-term multiple dosing may introduce extreme complexity, especially if all of these factors combine within a single drug example. And long term dosing (see next section) opens up the possibility of variations occurring during therapeutic regimens that do not occur with single doses, and disease opens up possibilities of variations caused by disease, and by the drug interactions that occur when multiple drugs are used in the individual patient. For all of these reasons, new drug discovery programmes are usually designed to produce new treatments that conform to the simplest models.

13.3.2 The fundamental multiple-dose concentration–effect relationship

This is represented in Figure 4.2. Again, no presumptions are made about particular kinetics applying, except that, in this case, elimination occurs by first-order processes. The effect is shown as first occurring when the plasma concentrations first rise above the threshold for effect, during, in this case the third dosage interval – continuous effect is established during the fifth dosage interval. The concentrations fluctuate between a maximum and a minimum, as described in earlier chapters, both of which are below the threshold for unwanted effects and above the threshold for desired effect.

The fundamental models shown in Figures 4.1 and 4.2, illustrated in part by the examples in this chapter, together with the observations of Gerhard Levy, provide an excellent starting point for our excursion into the world of PK/PD modelling, the principal topic of the next chapter.

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14

Pharmacokinetic/Pharmacodynamic Modelling: Simultaneous Measurement of Concentrations and Effect

14.1 Introduction

The objectives of modern analysis of drug action are to delineate the chemical or physical interactions between drug and target cell and to characterize the full sequence and scope of actions of each drug (Ross, 1996). This involves integrating the dose–response relationships considered in the previous chapter with time–action considerations.

In Chapter 4, and again in the previous chapter, we showed that, after single doses of drugs, while concentrations in plasma increase and decrease, so effects are presumed to increase and decrease. This is a fundamental expectation. No particular models, linear or non-linear need to be invoked in stating this principle, which can be considered descriptively. However, we can now examine in greater detail the ways in which this principle does and does not apply, and study the application of mathematical models to what has come to be known as the pharmacokinetic/pharmacodynamic (PK/PD) relationship.

A number of relevant scientific and medical observations date from before the formal organization of parallel PK and PD research. For example, it has long been known that:

- The effect may be closely related to the concentration in plasma so that the time of maximum concentration and effect coincide (e.g. i.v. thiopental, with which induction of effect is virtually instantaneous, and oral carebastine).
- The time of maximum effect can precede the time of maximum concentration (e.g. alcohol, glutethimide and isoprenaline).
- The time of maximum effect can occur later than the time of maximum concentration (e.g. LSD and warfarin).
- In some single dose cases there is an expectation of a permanent effect (e.g. treatment of a headache with an analgesic).
- The effect of a drug can be undetectable after a single dose, only appearing during multiple dosing therapy, but not obviously related to the growth of the plasma concentrations towards the pharmacokinetic steady-state (e.g. antibacterial drugs, and those used in epilepsy and psychiatry).

In this chapter we present model relationships of various different types between observed concentration and effect. Some of the examples chosen for this chapter are descriptive, with no mathematical models. Also,

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some of the mathematical models are presented with no applications. The objective is to illustrate the general principles applicable in key examples from what is now, a considerable volume of literature.

14.2 PK/PD modelling

14.2.1 Objectives

- To describe the time-courses of concentrations and effects in mathematical terms.
- To derive equations for concentration/response relationships at sites of action.
- To explain time-dependent relationships in mechanistic terms.
- To generate the ability to make predictions of dose/effect relationships, effect of changing dosage regimens etc.
- To facilitate comparisons between different drugs and selection of optimal compounds in structure/activity work.
- To provide methods for the study of drugs for which there are no bioanalytical methods.

14.2.2 Single-compartment, time-independent PK/PD models

Although it is reasonable to expect a modified form of the E_{max} model (Equation 13.3) to apply, *in vivo* the range of concentrations may be limited and simpler equations can be appropriate, particularly if the concentrations are on the lower, almost linear, part of the dose–response curve [Figure 13.1(a)] The simplest model is where (i) the drug distributes into a single compartment, represented by plasma, and (ii) the effect is an instantaneous, direct function of the concentration in that compartment. In this situation, the relationship between drug concentration (C) and a pharmacological effect (E) can be simply described by the linear function:

$$E = SC \tag{14.1}$$

where S is a slope parameter. If the measured effect has some baseline value (E_0), when drug is absent (e.g. a physiological effect such as diastolic blood pressure or resting tension on the tissue in an organ bath), then the model may be expressed as:

$$E = E_0 + SC \tag{14.2}$$

The parameters of this model, S and E_0, may be estimated by linear regression. This model does not contain any information about efficacy and potency, cannot identify the maximum effect, and thus cannot be used to find the concentration for 50% effect or for a defined effect in 50% of patients (EC_{50}). At higher concentrations, plotting log(concentration) commonly makes the data linear within the approximate range 20–80% of maximal effect [Figure 13.1(b)]. This log transformation facilitates a graphical estimation of the slope (m) of the apparently linear segment of the curve:

$$E = m\ln(C_0 + C) \tag{14.3}$$

where C_0 is the baseline concentration (usually zero, but not for cases of add-on therapy or when administering molecules that are also present endogenously). In this equation, the pharmacological effect may be expressed, when C is zero, as:

$$E_0 = m\ln C_0 \tag{14.4}$$

As implied earlier, for larger ranges of concentration it may be necessary to use the E_{max} model (Equation 13.3). This allows the computation of an EC_{50}; and when two or more compounds are investigated, comparison of potencies. If there is a baseline response (E_0), then this may be added:

$$E = E_0 + \frac{E_{max} C^{\gamma}}{EC_{50}^{\gamma} + C^{\gamma}} \tag{14.5}$$

As before (Section 13.2) the sigmoidicity parameter or Hill coefficient, γ, accounts for situations when the slope of the curve is greater or less than 1. At the molecular level, $\gamma > 1$ indicates cooperativity of binding; indeed Hill introduced the coefficient to explain the binding of oxygen to haemoglobin ($\gamma \sim 2.8$). However, *in vivo* it is more difficult to explain why the value of the Hill coefficient is what it is. The slopes of dose-response curves vary between subjects, and some of the variation may reflect differences in plasma protein binding, as it is generally the non-bound drug that can diffuse to the site of action. From a practical point of view, the larger the value of the exponent, the steeper the dose–response curve. A very high exponent can be viewed as indicating an all-or-none effect (e.g. the development of an action potential in a nerve). Within a narrow concentration range, the observed effect goes from all to nothing or vice versa.

The equation equivalent to Equation 14.5 for the relationship between concentration and effect for an antagonist is:

$$E = E_0 + \frac{I_{max} C^{\gamma}}{IC_{50}^{\gamma} + C^{\gamma}} \tag{14.6}$$

where IC_{50} is the concentration causing 50% inhibition.

In vivo, these models, analogous to the classical dose or log dose–response curves of *in vitro* pharmacology, are limited to direct effects in single-compartment systems. These models make no allowance for time-dependent events in drug response.

14.2.3 Time-dependent models

The most common approach to *in vivo* PK/PD modelling involves sequential analysis of the concentration versus time and effect versus time data. The kinetic model provides an independent variable, such as concentration, *driving* the dynamics. Only in limited situations could it be anticipated that the effect influences the kinetics, for example, effects on blood flow or drug clearance itself.

Levy (1964), Jusko (1971) and Smolen (1971, 1976) described the analysis of dose–response time data. They developed a theoretical basis for the performance of this analysis from the data obtained from the observation of the time course of pharmacological response, after a single dose of drug, by any route of administration. Smolen (1976) extended the analysis to the application of dose–response time data for bioequivalence testing.

In dose–response–time models, the underlying assumption is that pharmacodynamic data give us information on the kinetics of drug in the *biophase* (i.e. the tissue or compartment precisely where the drug exhibits its effect). In other words, apparent half-life, bioavailability and potency can be obtained simultaneously from the dose–response–time data. Considering such a model, assuming (i) first-order input/output processes and (ii) extravascular dosing, the kinetic model then drives the effect function of the dynamic model. It is the *dynamic behaviour* which is described by the response model. A zero-order input and first-order output governs the *turnover* of the response. This permits consideration of situations where the plasma concentration represents delivery of the drug to an effect compartment; the time course of drug concentration and of effect (both in the biophase) is different from that simply observed in plasma concentrations.

14.2.3.1 Ebastine and carebastine

Ebastine is a novel H_1-antagonist. It is extensively metabolized to its carboxylic acid analogue carebastine. Investigations into the pharmacokinetics, the plasma concentrations, and the effects of carebastine, which appears to account for most, if not all, of the pharmacological potency, were conducted in healthy volunteers after oral doses (Vincent *et al*. 1983). The pharmacokinetics exhibited exponential growth and decay, probably reflecting a balance of formation from the ebastine and the elimination of the carebastine. The authors calculated an elimination half-life of 10–12 hours. The pharmacodynamic effect studied was percentage of the wheal area induced in a standardized trauma test, compared with placebo. The time to maximum wheal inhibition, which occurred between 2 and 6 hours after dosing with ebastine, corresponded with the time to peak plasma concentration of carebastine. The plasma concentrations were linearly and significantly correlated with the absolute percentage of the histamine-induced wheal area in some but not all of the subjects (Figure 14.1). Thus, if a hysteresis curve (Section 14.2.4) were to be drawn with the best of these data, it would fit the model B_1 of Figure 14.3. The most appropriate mathematical model would be one of the simplest of the equations, Equation 14.1. However, note that the wheal area was not 100% at the earliest time point, when the concentration was presumably zero, suggesting that Equation 14.2 would be more appropriate. This might have reflected experimental variation, or it could have reflected a small contribution to the effect by the unchanged drug, ebastine, at the earlier time points.

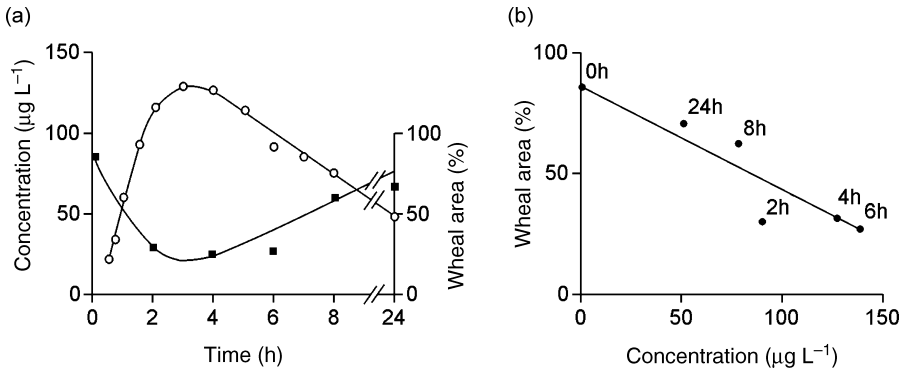

Figure 14.1 (a) Time course of the plasma concentrations of carebastine (open circles) and the histamine-induced wheal area (closed squares) in a representative subject after a single oral dose of 10 mg. of ebastine. (b) Relationship between plasma concentration and effect – the times of collection are shown. (Redrawn from Vincent *et al.*, 1988.)

14.2.3.2 Unequal distribution within plasma: ethanol and glutethimide

With regard to ethanol, it is now well-established that:

- The effect of alcohol is greater during the rising phase of the blood alcohol–time curve (i.e. when absorption is taking place). This is commonly called 'acute tolerance'.
- There is a concentration gradient during absorption with highest concentrations in the hepatic portal vein, intermediate concentrations in the circulation to the brain, and lowest concentrations in the antecubital vein, the usual site of blood sampling (all three are similar once equilibrium is reached).
- Alcohol crosses all membranes through pores, and its volume of distribution, including brain, is total body water, so a one-compartment pharmacokinetic model is appropriate for most purposes.

- The effects are unexpectedly high, per unit of blood concentration, during the early phase, because of the site of sampling (Table 14.1). This almost certainly applies to all orally administered centrally acting drugs, during the acute phase of oral dosing, including hypnotics in particular.

Table 14.1 Ethanol effects on the ascending and descending phases of the blood ethanol curve; Shipley–Hartford Abstraction Scale, errors of omission (Jones and Vega, 1972; Curry, 1980)

Group	Mean score ± SD
Ascending phase	2.8 ± 2.3
Descending phase	0.6 ± 0.8

F-ratio = 7.56 ($p < 0.01$).

An appropriate PK/PD model for this case would be a model of the type in Equation 13.3 showing saturation (a maximum possible effect). However, many different measures are used to evaluate the effects of alcohol, including ratings of overt behaviour and psychomotor tests, some of which would have a baseline value. At low doses an apparent excitatory response may especially be seen. This also occurs in the initial phase following any dose. Additionally, different tests are needed for evaluation of mid-range moderate impairment and high dose stupor, so both Equations 14.5 and 14.6 will be applicable dependent on circumstances.

Analogous observations have been made with glutethimide (Figure 14.2). The ability of a subject to follow a moving light was studied with the subject's head in a fixed position (smooth tracking test). The inhibition of this ability reached its peak when the concentration of glutethimide was still rising. The peak concentration coincided with almost total disappearance of effect. It is probable that this, as with the alcohol observation, arose from inhomogeneity of drug concentrations in plasma. This phenomenon was extensively documented and reviewed by Win Chiou in 1989 (Section 7.9). A similar result is observed when the effect is rapidly neutralized by physiological reflex mechanisms, as with isoprenaline (see later). As already mentioned in relation to alcohol, this is sometimes termed acute tolerance.

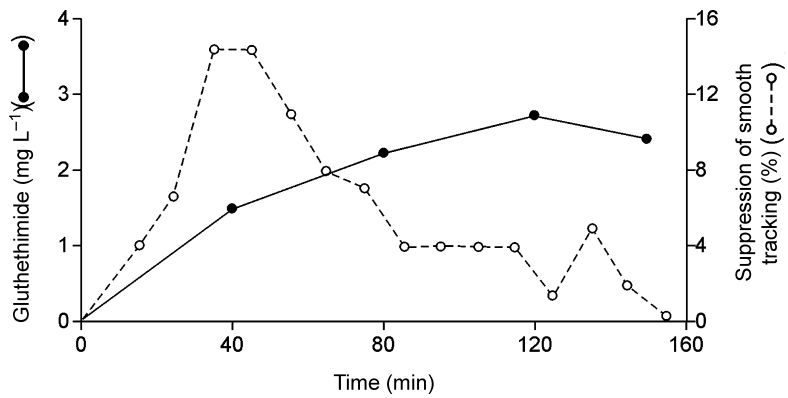

Figure 14.2 Plasma concentrations of glutethimide and percentage suppression of smooth tracking. (Redrawn from Curry & Norris, 1970.)

14.2.4 Hysteresis

The word hysteresis is derived from the Greek, meaning 'deficiency' or 'lagging behind'. It was coined by James Ewing to describe ferromagnetism – after removal of the magnetizing force the metal remains magnetized and only becomes non-magnetized very slowly. The crux of hysteresis is that the effects cannot be predicted from the input alone, it is necessary to know the current state of the system and for that, one needs to know the previous state. Thus, working from the standard growth and decay model for effect and for plasma concentrations, it is possible to plot effect (*y*-axis) against plasma concentrations (*x*-axis). If a line is drawn linking the data points *in the order in which they were recorded* a construction line of one of the four types in Figure 14.3. is derived.

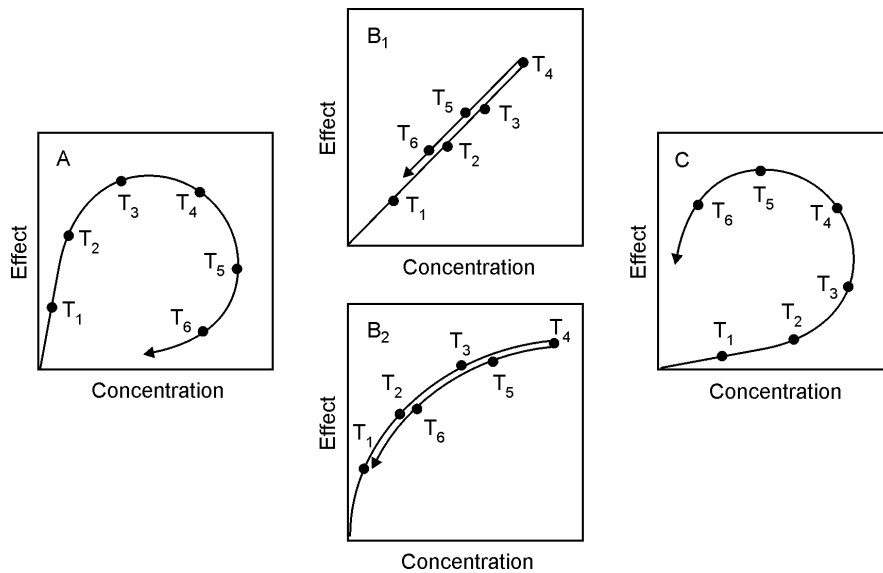

Figure 14.3 Model curves. A – clockwise hysteresis, B_1 – no hysteresis, straight line relationship, B_2 – no hysteresis, saturation evident, C – anticlockwise hysteresis. In the view of some experts, Case A should be termed "proteresis".

Hysteresis curve (A) is described as a clockwise hysteresis curve. It shows an early intense effect occurring at relatively low concentrations in plasma. As time goes by, the effect becomes maximal and then decreases before the plasma concentrations return to zero. This can occur when distribution to tissues plays a large part in the time course of the action of the drug, such as with alcohol, or when physiological mechanisms cause the effect of the drug to wear off while the drug is still present, as with isoprenaline (Figure 14.4).

Curve (C) is an anticlockwise hysteresis curve. The effect develops relatively slowly so that early high plasma concentrations elicit disproportionately small effects. This occurs when the drug effect is caused by an active metabolite, or when the receptors are in a slowly perfused compartment, or when there is a specific effect compartment, or when the effect that is measured is dependent on a sequence of biochemical changes (e.g. warfarin), or when the effect is on behaviour such that the drug initiates a change in for example perception, which takes time to be reflected in overall behaviour (e.g. chlorpromazine).

Curves (B_1) and (B_2) are the ones expected according to pharmacological principles, where hysteresis is not a confounding factor. They are rarely seen. Note that in this figure we have shown a graph of effect versus

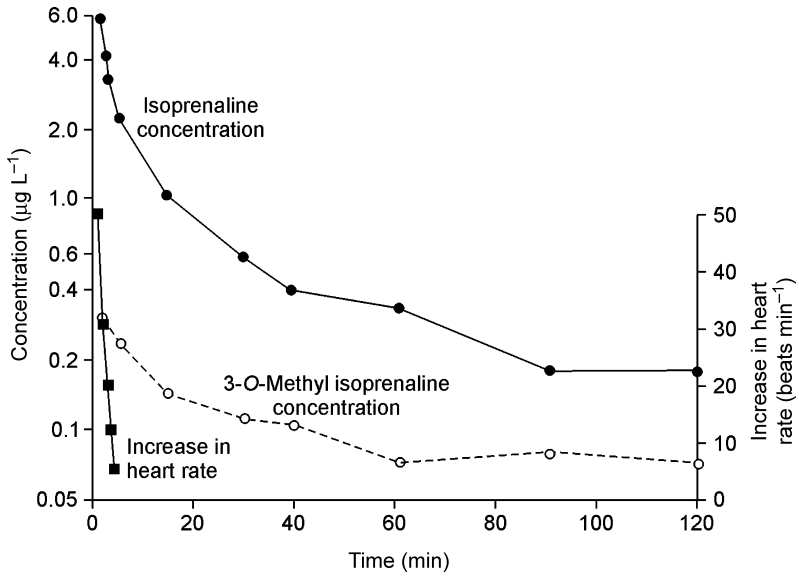

Figure 14.4 Concentration–effect relationship for isoprenaline in a dog given 0.64 μg kg^{-1} intravenously. (Redrawn from Conolly *et al.*, 1971.)

concentration, not log(concentration). There is a near linear effect/concentration relationship in B_1, of the type that would be expected if the effect was measured at the lower left hand end of a conventional dose–effect curve, and B_2 exhibits the potential result of studies conducted at higher concentrations. As mentioned earlier, Figure 14.1. (carebastine) shows data on which a relationship of his kind (B_1) would be observed, restricted in the study quoted to the lower portion of the curve, where the effect is basically linearly related to concentration.

14.2.5 Pharmacokinetic distribution models

These models take into account the universal fact that even when a drug is delivered intravenously into a vein; it is not instantaneously at equilibrium between plasma and its site of action. There will be cases where the practicalities of experimental design dictate that there is no deviation from a close relationship between the time courses of effect and plasma concentration, such as with carebastine (above), but more commonly phenomena that are described in this section occur.

14.2.5.1 Thiopental and propofol

Thiopental is presented as the archetype intravenous anaesthetic, developed during the 1950s for use in military arena surgical hospitals (MASH) in particular. Thiopental shows redistribution after i.v. doses with a prominent α-phase occurring while the drug is distributing into one or more peripheral compartments. Clinically, a series of serially smaller doses every 20 minutes or so were needed to maintain anaesthesia with this drug, or it could be given as a continuous infusion with a gradually reducing rate.

Thiopental has been virtually superseded by more modern drugs, of which propofol is probably the most studied. The pharmacokinetic phenomena of the two drugs are similar, with the complication that propofol is formulated in excipients/solvents that must themselves be administered with great caution by slow

intravenous infusion. There has been extensive PK/PD modelling with propofol; some of the characteristics being:

- Dosing by slow intravenous infusion.
- A central 'pool' or compartment with two sub-pools:
  – a rapidly equilibrating pool, which includes the brain
  – a slowly equilibrating pool, which includes fat.

Thus the situation with propofol is analogous to observations made with thiopental (see Figure 5.8), and it leads to a similar result. The relationship between effect and concentration in the rapidly-equilibrating pool would be describable with an equation relating intensity of effect to concentration in plasma. With thiopental, it is believed that no more than 2 minutes are needed for the i.v. administered drug to penetrate the brain and reach its receptors, and because the i.v. injection is given over a 5 minute period or longer, the brain and plasma are viewed as a single compartment. The effect occurs almost instantly, and declines with the decline in plasma concentrations. Thus, perhaps surprisingly, for thiopental, a highly lipid-soluble drug showing multi-compartment pharmacokinetics, and a high apparent volume of distribution, the receptors are considered to be in the central compartment, and equations closely relating the effect to the concentration in plasma are in order. It is of interest to compare this, conceptually, with expectations for the chemically-related drug, phenobarbital, which is highly polar, which appears to show one-compartment pharmacokinetics from its plasma decay curve, and which has an apparent volume of distribution that is not much different from total body water. However, it crosses the blood–brain barrier slowly, in relatively small quantities, in accord with the existence of a small and specific peripheral compartment that is in fact its site of action. In this case, the effect on the brain develops slowly after single doses, including those given by i.v. injection. In modelling terms an alternative model is needed for this drug, with an 'effect' compartment (the brain) that involves amounts of drug that are not large enough to purturb the plasma concentrations (see later sections).

14.2.6 Receptors in the peripheral compartment models

14.2.6.1 LSD

Wagner and colleagues (Wagner, 1968; Wagner *et al*., 1968) showed that, after i.v. injections of lysergic acid diethylamide (LSD), the concentrations of LSD showed the typical bi-exponential decay associated with distribution through a two-compartment system. During the initial α-phase of decay, during which the drug was transferring from the plasma and other parts of the central compartment to the peripheral compartment, the effect, assessed using an arithmetical performance test, was rising. At the same time, the calculated concentrations in the peripheral compartment were rising. The apparent volume of the central compartment was $0.163\,\mathrm{L\,kg^{-1}}$ (approximating to extracellular fluid) while the apparent volume of the peripheral compartment was $0.155\,\mathrm{L\,kg^{-1}}$ – this compartment presumably included the intracellular fluid of the brain. There was a linear relationship between effect and the concentration in the peripheral compartment, with a baseline performance score. The data are shown in Figure 14.5. The model of Equation 14.2 would be appropriate in this case, with a clockwise hysteresis curve with no saturation.

14.2.6.2 Digoxin

There have been several studies of the multi-compartment nature of the distribution of digoxin after i.v. doses, and the delay in onset of useful effect after such doses is well-known to clinicians. Historically, there was a practice of digitalization – administration of the maximum possible tolerated dose followed by reduction of the dose to a more acceptable level, and there has been a need to devise a more logical approach

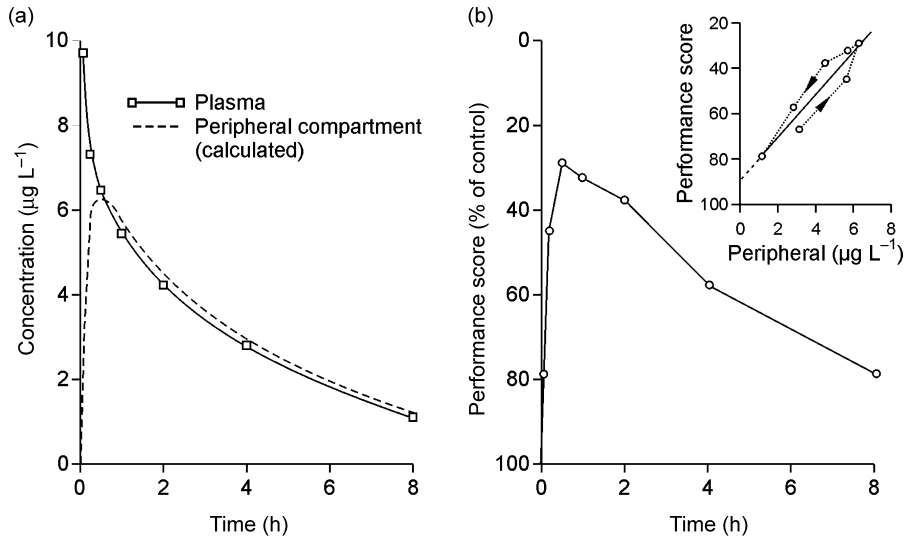

Figure 14.5 (a) Mean plasma concentrations of LSD in five individuals following i.v. bolus doses of 2 μg kg^{-1}, together with calculated concentrations in the peripheral compartment. (b) Performance score based on arithmetic tests in the same experiment. The insert in (b) shows the performance score plotted against concentration in the peripheral compartment, indicating a straight line relationship with evidence of modest hysteresis. (Redrawn after Wagner *et al.*, 1968.)

to determination of the optimum dose. PK/PD has helped to devise an answer. Typically such studies involve the inotropic effect being measured as systolic time interval.

Reuning *et al.* (1973) used a two-compartment model to describe the kinetics of digoxin, showing that the inotropic effect related more closely to the concentrations in the peripheral compartment than to those in plasma. In later studies, other investigators demonstrated the use of three-compartment models showing that there was a slightly better correlation between effect and a third, 'deeper' (slowly distributing) compartment.

Because the receptors for digoxin are in the heart, this provides an example of slow penetration to receptors in the most highly perfused tissue in the body. The sarcoplasmic reticulum of the cardiac cell is presumed to be the site of the receptors. The equilibrium takes as much as 5 hours to be achieved, which is many multiples of the half-life of the α-phase. At equilibrium, the majority of the body content of the drug is in the peripheral compartment. This was checked with studies of renal elimination to ensure that the drug thought to be in the body had not been excreted. It may be that this presaged the concept of an 'effect' compartment, but it should be noted that the proposal for digoxin kinetics arose from the analysis of concentrations in plasma (see later).

A graph of $\Delta(Q - S_2)$ against fraction in the tissue compartment was linear, and the intercept was not significantly different from zero (Figure 14.6). Thus an appropriate model to relate drug in the peripheral compartment with effect is Equation 14.1. The data are insufficient to determine whether or not there was a hysteresis effect in this study.

Reuning *et al.*, (1973) discussed the post-equilibration phase, noting that up to 13 hours could be needed to reach this point. After this point, changes in effect parallel plasma concentrations. This work had practical consequences:

- The recognition that V is lower in renal failure patients and that they need lower doses.
- The use of a lower loading dose in such patients, instead of digitalization.
- The taking of clinical monitoring samples 12 hours after the dose.

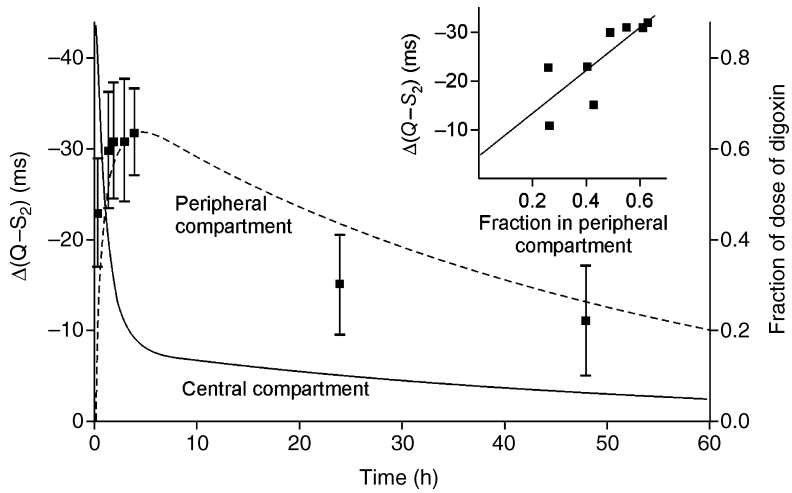

Figure 14.6 Relationship of the change in the $Q-S_2$ interval, $\Delta(Q-S_2)$ to computer-simulated curves for fraction of digoxin dose in the central and peripheral compartments as a function of time after a single intravenous dose of digoxin. Data are mean ± SEM from six normal subjects. Inset: plot of intensity of pharmacological effect as function of fraction of drug in peripheral compartment.

More recently, interest in the pharmacokinetics and pharmacodynamics has turned to the possibility of there being a specific 'effect' compartment, in addition to the distribution compartments.

14.2.7 Effect compartment models

These models are sometimes called 'link models' or 'effect-distribution models'. They facilitate estimation. of the *in vivo* pharmacodynamic effect from non-steady-state effect (E) versus time and concentration (C) versus time data, within which potential exists for observed E and C to display temporal displacement with respect to each other (Segre, 1968; Wagner, 1968; Dahlstrom *et al.*,1978; Sheiner *et al.*,1979). The rate of change of amount of drug (A_e) in a hypothetical effect compartment can be expressed as:

$$\frac{dA_e}{dt} = k_{1e}A_1 - k_{e0}A_e \tag{14.7}$$

where A_1 is the amount of drug in the central compartment of a pharmacokinetic model, linked to the effect compartment, with first-order rate constants k_{1e} and k_{e0} (Figure 14.7). Note the use of the same convention of labelling the parameters, e represents the effect compartment.

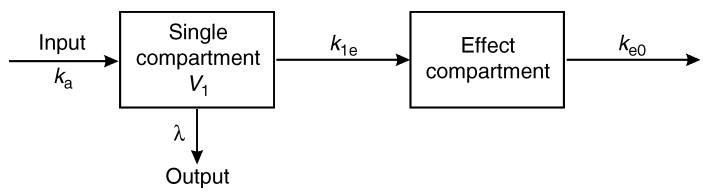

Figure 14.7 The one compartment distribution model of earlier chapters shown with the addition of an effect compartment.

The corresponding expression for the amount of drug in the effect compartment, for a one-compartment model with bolus input of dose (D) is:

$$A_e = \frac{k_{1e}\,D}{k_{e0}-\lambda}\left[\exp(-\lambda t)-\exp(-k_{e0}t)\right] \tag{14.8}$$

where λ is the elimination rate constant. The concentration of drug in the effect compartment, C_e, is obtained by dividing A_e by the effect compartment volume V_e:

$$C_e = \frac{k_{1e}\,D}{V_e(k_{e0}-\lambda)}\left[\exp(-\lambda t)-\exp(-k_{e0}t)\right] \tag{14.9}$$

At equilibrium, the rates of drug transfer between the compartments are equal:

$$k_{1e}\,A_1 = k_{e0}\,A_e \tag{14.10}$$

$$k_{1e}V_1C_1 = k_{e0}V_eC_e \tag{14.11}$$

If the partition coefficient, K_p, equals C_e/C_1 at equilibrium (steady-state), then rearranging Equation 14.11 gives:

$$V_e = \frac{k_{1e}V_1}{K_p\,k_{e0}} \tag{14.12}$$

Substituting Equation 14.12 for V_e in Equation 14.9 yields:

$$C_e = \frac{k_{e0}\,DK_p}{V_1(k_{e0}-\lambda)}\left[\exp(-\lambda t)-\exp(-k_{e0}t)\right] \tag{14.13}$$

At equilibrium, C will be equal to C_e/K_p, so dividing both sides by K_p and substituting C:

$$C_1 = \frac{k_{e0}\,D}{V_1(k_{e0}-\lambda)}\left[\exp(-\lambda t)-\exp(-k_{e0}t)\right] \tag{14.14}$$

This is how the link-model relates the kinetics in plasma to the kinetics of drug in the effect compartment. When used together with the E_{max} model for estimation of the maximal drug-induced effect, the concentration at half-maximal effect (apparent EC_{50}) and the rate constant of the disappearance of the effect (k_{e0}):

$$E = E_0 + \frac{E_{max}C_e}{EC_{50}+C_e} \tag{14.15}$$

assuming the sigmoidicity factor (γ) to be equal to unity. Computer fitting of the equations to the effect data allows estimation of the rate constant for the disappearance of the effect, k_{e0}, EC_{50} and E_{max}.

At steady state, C_e is directly proportional to the plasma concentration (C), as $C_e = K_pC$. Consequently, the potency (EC_{50}) obtained by regressing the last two equations represents the steady-state plasma concentration producing 50% of E_{max}.

Note that the effect rate constant (k_{1e}) may be viewed as a first-order distribution rate constant. It assesses the rate of delivery of the drug to a specific tissue, determined by, for example, tissue perfusion rate,

apparent volume of the tissue and eventual diffusion into the tissue. It should be emphasized that the link model applies to situations where a small but pharmacologically significant subset of the dosed molecules penetrates a separate compartment with its own input-output characteristics, distinct from anything observable in the plasma concentration decay curve or available for calculation as in the case with the pharmacokinetic distribution models (contrast LSD, and digoxin as an example of a compartment distribution model application). Literally hundreds, perhaps thousands, of cases, especially in regard to drugs acting within the cardiovascular system, such as depicted in Figure 14.8 have been described.

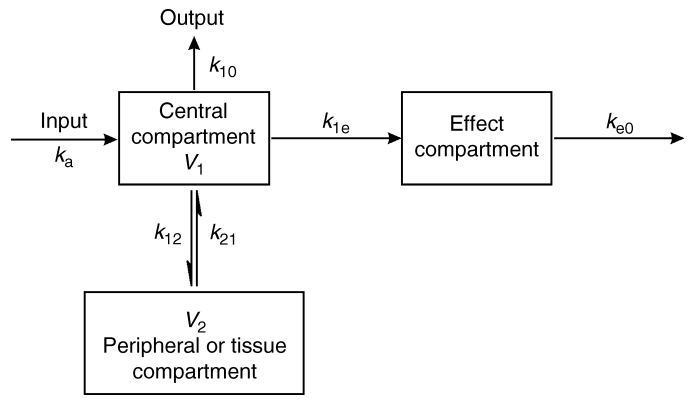

Figure 14.8 Representation of a link model applied to a drug that confers the characteristics of two-compartment model.

A tabulation of some of the times to equilibrium reported appears as Table 14.2. This model is now established as indicating a fundamental mechanism of pharmacology.

Table 14.2 Equilibration half-lives determined using the effect compartment model

Drug	Equilibration half-time (minutes)	Pharmacological effect
Disopyramide	2	QT prolongation
Verapamil	2	PR prolongation
N-Acetylprocainamide	6.4	QT prolongation
Quinidine	8	QT prolongation
Digoxin	214	LVET shortening
Ergotamine	594	Vasoconstriction

QT and PR are electrocardiographic intervals; LVET is left ventricular ejection time.

It is of interest that digoxin, a drug that has been extensively studied in this context, has blurred the distinction between the distribution compartment models and the effect compartment models. A similar comment could be made in relation to phenobarbital. The effect compartment model has been very successful in exploring a large number of pharmacological observations, and it has achieved a position of near universality in its position as describing a fundamental mechanism of pharmacology, finding application with single and multicompartment drugs with long equilibration half-times, to drugs with such short equilibration half-times that they are effectively zero.

Lorazepam has provided us with a remarkable demonstration of the power of PK/PD modelling with an effect compartment. Gupta *et al*. (1990) used a battery of psychomotor and cognitive tests in a group of subjects given oral lorazepam and compared the data with plasma concentrations of the drug. The plasma concentrations were best described by a two-compartment model with first-order absorption. There was an anticlockwise hysteresis loop for each effect. Fitting the time-course of the concentrations in an integrated PK/PD model required an effect compartment with a finite equilibrium rate constant between it and the plasma compartment. The magnitude of the temporal lag was quantified by the half-life of equilibration, and the CNS effect was characterized by a mean estimate of maximum predicted effect. Sigmoid concentration–effect curves were generated relating the concentration in the effect compartment and the measured pharmacological effects (Figure 14.9).

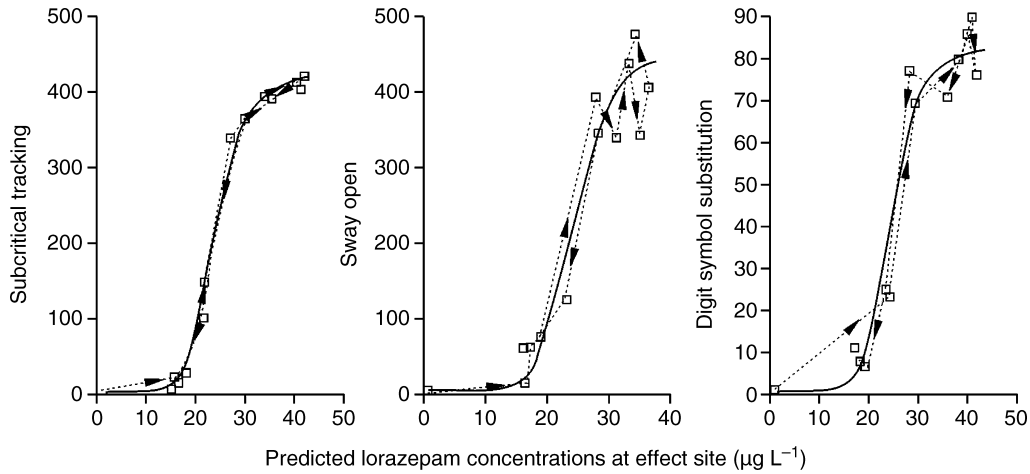

Figure 14.9 Relationship between predicted effect site concentration (C_e) of lorazepam (□) and three psychomotor effects. Solid-lines fitted to the PK/PD model as a function of C_e; arrows show hysteresis. (Redrawn from Gupta *et al.*,1990.)

14.2.8 Warfarin type models

Effect compartment and link models are limited by their applicability to situations in which the equilibrium between plasma and response is due to drug distributional phenomena. In reality, there is often a delay between occurrence of maximum drug concentrations at the site of action and maximum intensity of effect, caused by slow development of the effect rather than slow distribution to the site of action. In this situation, indirect or 'physiological substance' models are more appropriate (Dayneka *et al.,*1993; Levy, 1994; Sharma and Jusko, 1997). Warfarin is a good example. This drug inhibits the prothrombin complex activity (PCA), by its action on vitamin-K dependent activation of clotting Factors II, VII, IX and X, formed in the liver. The relationship between concentrations in plasma and effect is illustrated in Figure 14.10, which shows data for a single patient from among a group of five patients given oral doses of racemic warfarin (1.5 mg kg^{-1}). The peak plasma warfarin concentration was approximately 6 hours after the dose whereas the percent decrease in PCA, was maximal at approximately the 2-day point. Note that PCA, (or prothrombin time), is measured *in vitro*, as the time for blood to clot under controlled conditions, and normal values are in the region of 120 s. The therapeutic objective is commonly to increase this by approximately 70%, to ~200 s. This does not

reflect return to normality, but the achievement of a modified physiological state in which the risk of blood clotting *in vivo* is reduced. It therefore increases the risk of bleeding, and management of warfarin dosing involves careful manipulation and control of these two risks.

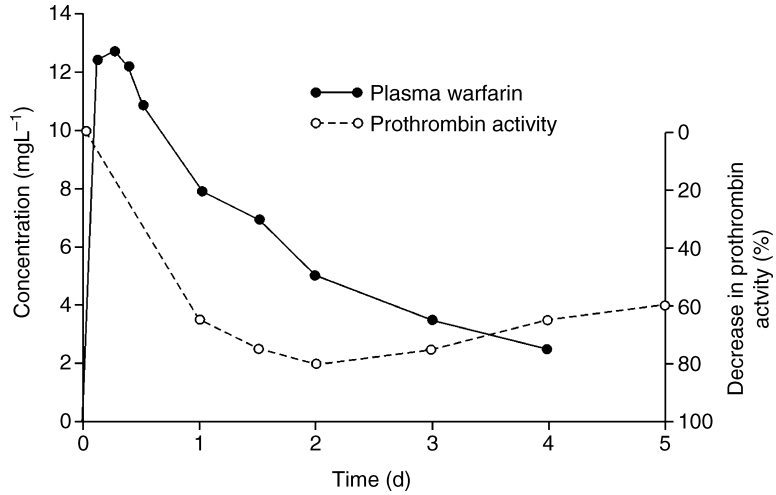

Figure 14.10 Plasma warfarin concentrations and depression of prothrombin activity after a single dose in one subject. (Redrawn after Nagashima *et al.,* 1969.)

Thus the effect of warfarin on the synthesis of the clotting factors begins to occur coincidentally with the appearance of the first molecules of the drug in the plasma, even after oral doses, as the effect occurs within the single pharmacokinetic compartment that apparently exists for this drug. However, because there is a considerable reserve of the clotting factors in the liver, by the time that the concentration of warfarin has reached its maximum (Figure 14.10), the decline of the reserve of clotting factors has only occurred to an extent of approximately 10%, as shown by the 10% increase in prothrombin time at this point, even though the drug concentration has been well above that needed to cause an effect for a considerable time. For the next 36–48 hours the synthesis remains blocked, and the clotting factor concentrations decline, causing further increases in the prothrombin time, after which the warfarin concentration declines further. The drug concentrations are now below the effective concentration, and the clotting factor concentrations begin to recover. This has major clinical implications, as anticoagulant activity is required as quickly as possible during a medical emergency, and so intravenous heparin is given as the first intervention, followed by oral warfarin.

In an investigation analogous to that of that of Figure 14.10, but using the more active (*S*)-enantiomer at a somewhat lower i.v. bolus dose (~10 mg), the concentrations of (*S*)-warfarin were described by the following exponential expression:

$$C = 1.05\exp(-0.0288t) \tag{14.16}$$

where C was measured in mg L^{-1} and t was measured in hours. Thus the (*S*)-warfarin half-life in this case was approximately 24 h. The effect was again maximal at 36–48 h, with a 60–70% reduction in PCA. Recovery was somewhat faster than in the example in Figure 14.10 – it was 80% complete after about 5 days. Note that the bioavailability of racemic warfarin is over 90%, and that the oral and i.v. doses result in the same time course of effect, in spite of very different time courses of drug concentrations in plasma. The apparent volume of distribution of racemic warfarin is in the region of 0.14 L kg^{-1} and the half-life varies over a range from 20 to 50 hours, with the half-life of (*S*)-warfarin and (*R*)-warfarin being, on average, approximately 32 and 43 h,

respectively. Accordingly, the clearance of the (*R*)-isomer is less than that of the (*S*)-isomer. The (*S*)-isomer is approximately three to five times more potent than the (*R*)-isomer.

Two further observations aid the understanding of the relationship between the pharmacokinetic and pharmacodynamic properties of warfarin. The dose in Figure 14.10 was a clotting factor synthesis blocking dose. In this circumstance, the changes in PCA can be used to evaluate the kinetics of the decline in concentrations of the clotting factors. It has been shown that this decline occurs monoexponentially, with a half-life, coincidentally with the warfarin half-life sometimes measured, of approximately 22 h, reaching a maximum of approximately 80% block at 48 h – no further increases in inhibition are seen, either with higher doses or at later time points [Figure 14.11(a)]. This figure is effectively a logarithmic transformation of the clotting data of Figure 14.10 over the first 36 h of the investigation.

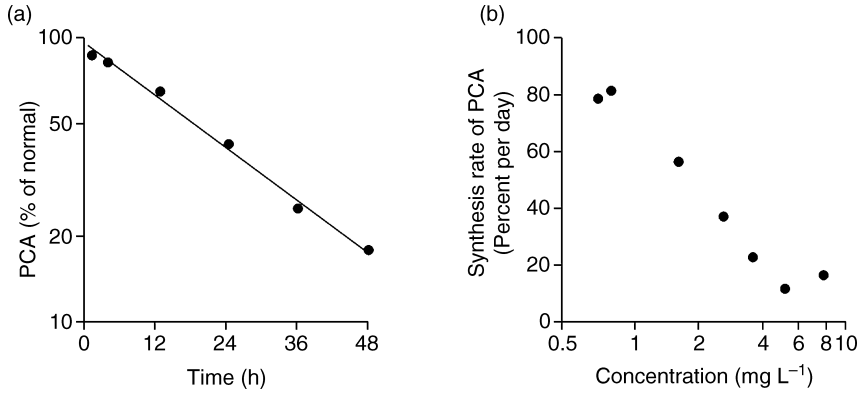

Figure 14.11 (a) Prothrombin complex activity declining exponentially over the first 48 hours after a synthesis blocking dose of warfarin sodium orally in a human subject. (b) Relationship between synthesis rate of the prothrombin complex activity (% d^{-1}) and plasma concentration of warfarin sodium. (Redrawn from Levy *et al.*, 1970.)

The second observation concerns the rate of synthesis of the clotting factors. A log(plasma concentration)–effect relationship with an IC_{50} of approximately 1.75 mg L^{-1} has been demonstrated for the racemate [Figure 14.11(b)]., where the effect is 'synthesis rate' of PCA (% day^{-1}). Data of this type are obtainable by dosing warfarin to the pharmacokinetic steady-state using different dose levels and measuring PCA once the steady-state is reached. The IC_{50} for (*S*)-warfarin is approximately 0.35 mg L^{-1}.

The PCA at steady state (PCA_{ss}) has been shown to be obtainable from:

$$PCA_{ss} = \frac{K_{in}}{k_d} \tag{14.17}$$

where K_{in} is the zero-order synthesis rate of the clotting factors, and k_d is the first-order rate constant of the decay ($\sim$0.03 h^{-1}) in Figure 14.11(a).

Equations have been derived to describe the turnover of the concentrations of the clotting factor(s) (dP/dt) (Nagashima *et al.*, 1969; Pitsiu *et al.*, 1993). Such equations incorporate k_d, and are complicated by the fact that PCA is increased when the synthesis rate of the clotting factors is reduced by the drug. The turnover rate of the clotting factors, assessed by means of PCA measurements, was 0.3 $s\,h^{-1}$. Warfarin, either as the racemate or the (*S*)-isomer reaches pharmacokinetic steady-state concentrations of approximately two to three times those achieved after single doses, within 2–3 days of initiation of treatment. This arises from the standard pharmacokinetic relationships between single and multiple doses discussed in Chapter 4. Thus, a reasonable target for steady-state plasma concentrations of racemic warfarin will be approximately

0.5–1 mg L^{-1}, achieving a 20–50% block of clotting factor synthesis, with the full effect evident within 2–4 days of initiation of therapy. This is achieved with long-term dosing with a wide range of oral doses in the range 1–10 mg day^{-1}. Monitoring of this scenario is usually achieved by means of PCA measurements, rather than drug concentration measurements.

14.2.9 Other examples

Two further examples of concentration–effect relationships provide insight into the complexity of quantitative pharmacology *in vivo*.

In the case of chlorpromazine, a group of newly diagnosed patients was observed over a period of forty days, during which they received a fixed regimen of 100 mg three times a day. The plasma concentrations rose and fell after each dose, and the overall plasma concentrations at first rose, as might be expected from the basic models of Figures 13.10 and 13.11, but then fell to a steady-state of approximately 30% of the highest concentration recorded – this is most evident from the trough levels. During this time, there was a steady development of the clinical effect (Figure 14.12), in keeping with the expectations of the psychiatrists at the time. Chlorpromazine has many metabolites, some of which share some of the activity of the parent drug, but there was no evidence in this study of metabolite involvement in the effect. Later studies also failed to reveal a robust metabolite contribution to the effect of chlorpromazine even with long-term dosing. From about the eighth day onwards, there was a strong *negative* correlation between the psychiatric score and the

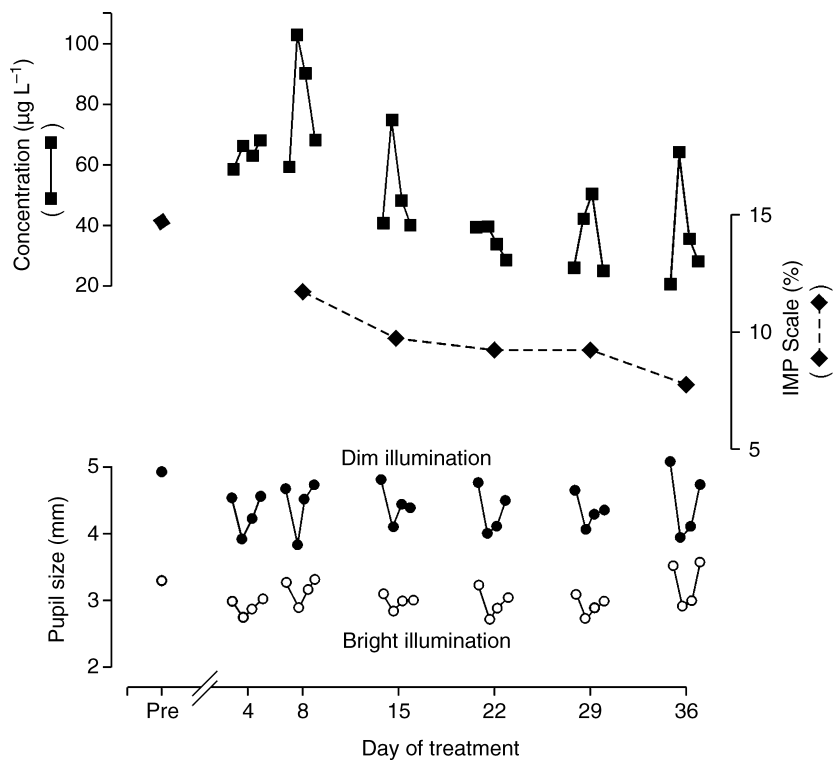

Figure 14.12 Mean plasma chlorpromazine concentrations, change in Inpatient Multidimensional Psychiatric Scale (% of maximum possible) and pupil size in 10 newly diagnosed patients receiving 100 mg every 8 hours. (Adapted from Sakalis *et al.*, 1972.)

concentrations in plasma. Pupil size is presented as an example of an autonomic nervous system effect which did show changes roughly in parallel with the drug concentrations.

Thus, Figure 14.12 illustrates several points already discussed, including enzyme induction and the difficulty of correlating effects in psychiatric patients to plasma concentrations, in part because of delayed effects and large contributions from placebo effects. A strong correlation between concentration and effect should not be expected for drugs designed to induce changes in cognition over relatively long periods of time.

The second example considers the treatment of bacterial infections with what Brodie described as 'a rational regimen of dosage', and to which Kruger-Thiemer applied a 'pharmacokinetic theory of dosage regimen' for sulfonamides. These concepts involve a loading dose followed by maintenance doses, designed to induce and maintain bacteriostatic concentrations for as long as is needed. This regimen yields a concentration curve at the site of action of the type shown in Figure 14.13.

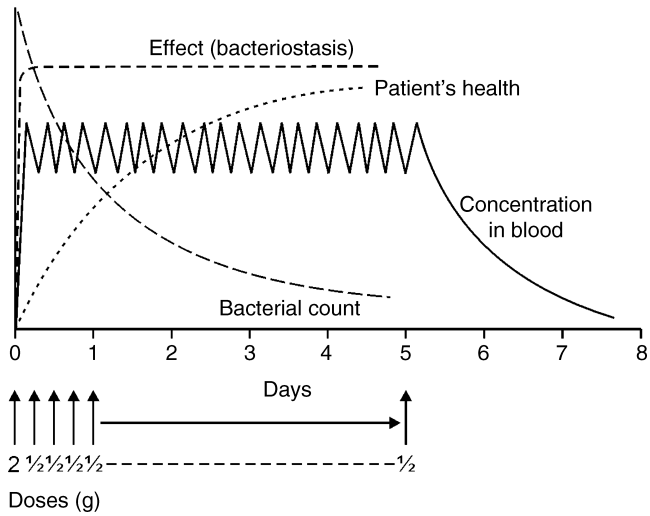

Figure 14.13 Time course of bacteriostatic chemotherapy. The figure shows drug concentrations in plasma induced by a loading dose, followed my maintenance doses for 5 days. The effect, bacteriostasis, the bacterial count, and the patient's feeling of well-being all show different time courses in this model.

While bacterial growth may be instantly inhibited, the bacterial count comes down more slowly, and the patient's feeling of improved health develops over a period of days. This figure is drawn as if for a sulfonamide with a loading dose of 2 g., and maintenance doses of 0.5 g. A basic feature of this diagram is that, with the dosing interval equal to the half-life of the drug, the concentration will fluctuate by 50% of the maximum. This type of regimen is very much used with drugs of all kinds. For example, treatment of joint pain with naproxen often involves a loading dose of two tablets followed by maintenance doses for several days of one tablet. Also, the monoclonal antibody, trastuzumab (Herceptin), is commonly used intravenously with a loading dose, followed by 3-weekly maintenance doses, for 6 months in order to suppress and keep suppressed any cancer cells that may have metastasized.

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