

DOSE-RESPONSE RELATIONSHIP AND THERAPEUTIC DRUG MONITORING

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INTRODUCTION

During the last 20 years, therapeutic drug monitoring (TDM) has become part of clinical management in several important areas of therapeutics. Basically, the usefulness of serum drug level monitoring stems from the fact that the dose-response relationship for many drugs shows a wide interindividual variability, which can be explained to a large extent by interindividual differences in pharmacokinetics. Under these conditions, the clinical effect correlates with the concentration of the drug in serum (which varies widely among individuals receiving the same dose) better than with the prescribed daily dose (1-3). When the effect is not immediately or easily quantifiable, e.g. in the case of antidysrhythmic or antiepileptic agents given prophylactically, knowledge of the serum drug concentration enables the clinician to make dosage adjustments more rapidly and effectively. By individualizing dosage based on TDM determinations, the variability in response which arises from interindividual differences in serum drug levels can be easily controlled.

There are important aspects of the dose-response relationship which need to be considered in TDM. If TDM is to be used rationally to make dosage adjustments, the following requirements must be met:

- i) the correlation between serum concentration and effect must have been clearly defined, and shown to be superior to the correlation between prescribed dosage and effect;
- ii) the intraindividual relationship between dosage and serum concentration must be known.

The purpose of the present article is to review knowledge concerning the dosage-serum level-effect relationships for some commonly monitored drugs and to highlight some of the implications resulting from variations in such relationships.

THE CONCENTRATION-EFFECT RELATIONSHIP

The concentration-response curve in TDM

In *in vitro* experiments, concentration-response curves for reversibly acting drugs are often relatively easy to construct and may be characterized by a typical S-shaped relationship with the drug level plotted on a log scale (4). If we extrapolate this model to the *in vivo* situation and separate the responses into those which are clinically beneficial (therapeutic effects) and those which are undesirable (dose-dependent toxic effects), we may obtain theoretical curves such as those depicted in Figure 1. Drugs which have a high therapeutic ratio allow attainment of a full therapeutic response at concentrations lower than those associated with toxicity, whereas in the case of drugs with a low therapeutic ratio the interval between therapeutic and toxic levels is much narrower. The therapeutic range can be defined as the concentration range at which substantial clinical benefits are observed in the absence of unacceptable side effects. In general, the monitoring of serum concentrations is more useful for drugs which have a low therapeutic ratio. In the case of drugs with high therapeutic ratios, in fact, the dosage can be increased on purely clinical grounds without fear of major toxicity.

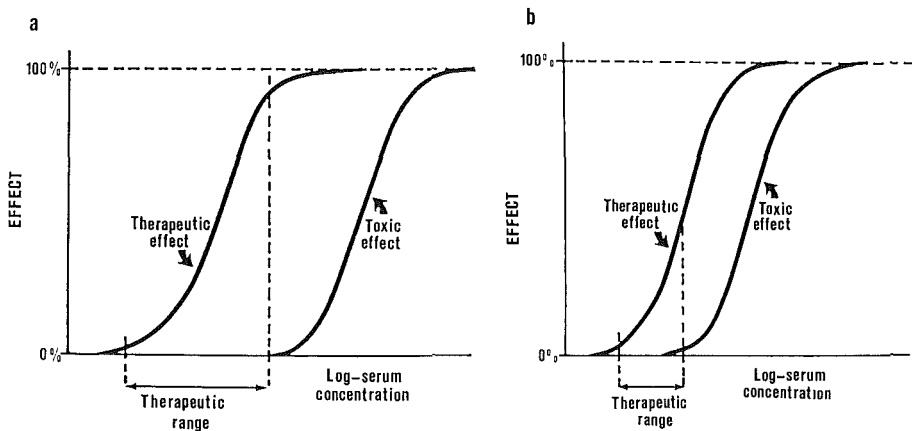


Figure 1. A simplified scheme of the relationship between serum drug concentration and therapeutic and toxic effects for drugs characterized by a high (a) or low (b) therapeutic index. In (a), the concentration required to produce 90% of the full therapeutic response does not cause toxic symptoms, whereas in (b) the same concentration produces marked toxicity. Modified from ref. 4.

In clinical practice, the situation is usually much more complex than that illustrated in Figure 1. In the first instance, therapeutic and adverse effects are usually difficult to quantify objectively and early appearance of toxicity often prevents exploration of the dose-response relationship over a sufficiently wide concentration range. Moreover, the concentration-response curve in the *in vivo* organism may be distorted by many factors, including the activation of physiological homeostatic mechanisms, changes in the levels of endogenous agonists, the involvement of more than one receptor type at target tissues and, at times, the occurrence of a slow equilibration phase between the drug in serum and the drug at the receptor sites (5). An additional complication, which will be discussed below in more detail, arises from the fact that the concentration-effect relationship may show a large interindividual and, sometimes, intraindividual variability.

An example of the problems which may arise when trying to define

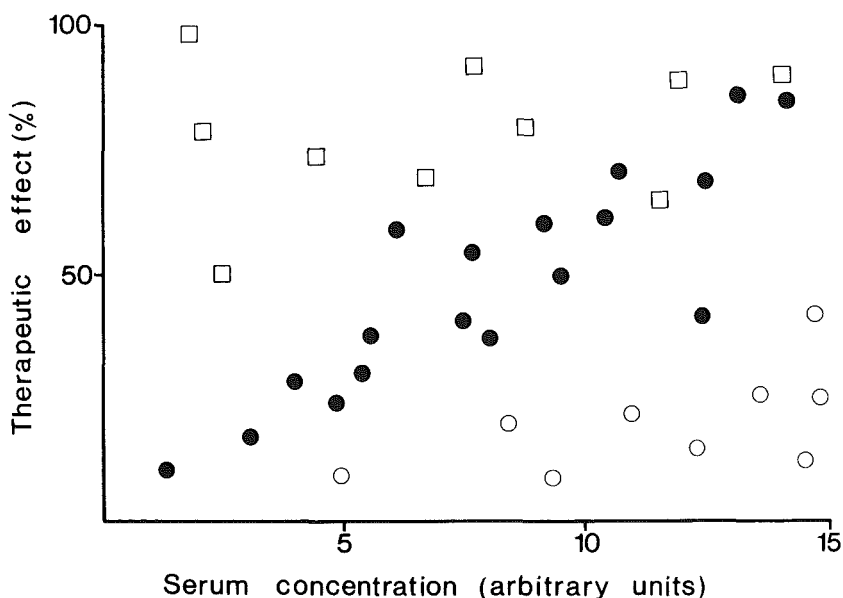


Figure 2. Example of the relationship between serum drug concentration and effect in a heterogeneous patient population which includes drug responders (•), non responders (○) and placebo responders (□). It is clear how inclusion of the latter groups masks the strong correlation between serum drug level and effect. Modified from ref. 6.

concentration-response relationships in clinical practice is given in Figure 2. Even when a drug shows a nicely graduated quantifiable dose-response curve, the overall concentration-effect relationship may be blurred or masked by inclusion into the trial of placebo-responders (patients who do well without the drug) and/or non responders. Sometimes, non-responders and placebo-responders can be identified beforehand and excluded from the trial but this may not be always feasible, resulting in failure to recognize the potential value of TDM in the subpopulation of patients showing a good response to the drug. Indeed, patients selection is the most critical factor to be considered in the study of dose-response relationships: therapeutic ranges identified in a given patient population may not be applicable to individuals with different kind of disease(s) and/or different severity of the same disease. The usually quoted therapeutic range of serum phenytoin (40-80 $\mu\text{mol/l}$), for example, was originally identified in patients with severe forms of epilepsy and it has been subsequently proved that many patients with milder forms of the disease can be optimally treated at serum phenytoin levels lower than these (7,8).

In order to use TDM effectively, it is important to obtain as much information as possible about (i) the shape of the intraindividual concentration-response curve, (ii) the interindividual variability in response and (iii) the factors which affect the intensity of response at a given drug concentration.

The shape of the curve

As discussed above, for many drugs the shape of the dose-response relationship may differ considerably from the prototype shown in Figure 1. The problems encountered in pharmacodynamic modelling in man and examples of different types of serum concentration-effect relationships for individual drugs have been recently reviewed (5). In some cases, the distortion of the relationship arises from pharmacokinetic factors: the serum level-response curve for a given drug, for example, may be affected by the simultaneous presence of an active metabolite, especially when the parent drug/metabolite ratio is dose-dependent. Another source of variation arises from changes in drug binding to serum proteins. Since the pharmacological response is generally considered to be proportional to the concentration of free (non protein-bound) drug, the relationship between total serum

concentration and effect can be distorted by concentration-dependent changes in unbound fraction (9). A situation of this kind is seen with disopyramide, whose binding to serum proteins decreases markedly with increasing drug concentration: therefore, any increase in total serum disopyramide concentration may underestimate the increase in concentration of free, pharmacologically active drug and, hence, magnitude of effect (10).

An important distortion of the dose-response curve, presumably caused by pharmacodynamic factors, is represented by "bell-shaped" relationships. For drugs which exhibit this relationship, the intensity of therapeutic effect increases with increasing serum drug concentration up to a maximum; thereafter, further increases in concentration result in paradoxical loss of clinical efficacy. The occurrence of this kind of relationship is by itself an indication for TDM, since it may be difficult to establish on purely clinical grounds whether a patient's lack of response is due to over- or under-dosing. A "bell-shaped" dose-response curve has been described for some tricyclic antidepressants and considered to be possibly related to antagonism of therapeutic effects by adrenergic blocking activity becoming manifest at high drug levels (11,12). A paradoxical decrease of efficacy at high drug levels, however, may occur with other compounds, including various anticonvulsants (13).

Variability in concentration-effect relationship

If the serum level-effect relationship was fixed and identical in all patients, the task of the clinician would be greatly simplified. It would be sufficient to draw a blood sample, measure the drug concentration and adjust dosage in order to obtain the optimal level. Unfortunately, in real life things are much more complicated. The main complication arises from the fact that, for virtually all drugs, there is not a fixed "optimal level" appropriate for all patients. On the contrary, there is considerable inter- and, sometimes, intra-patient variation in the response achieved at a given serum level: this implies that the "therapeutic range" should be regarded as a purely statistical concept, representing the concentration at which most (not necessarily all) patients with a well defined pathology will show an optimal response (1-4, 13,14). For some drugs, the inter-patient

variability in response is so great that subtherapeutic, therapeutic and toxic levels in a given population overlap widely: under these conditions, the definition of an optimal range becomes very difficult and the very value of monitoring serum levels is questionable. Interestingly, a criticism of this kind has been voiced for two of the most frequently monitored drugs, e.g. digoxin (15) and valproic acid (16).

Obviously, the fact that the relationship between serum level and response varies widely among individuals reduces the value of serum level monitoring, but it does not necessarily imply that TDM is useless in such situation. In fact, for some of these drugs it is still possible to identify empirically the serum level at which an individual patient shows the best clinical response (2,3,14): knowledge of this "individualized therapeutic range" provides a valuable reference which can be useful to evaluate the clinical picture should the same patient at a later stage show an unexpected change in response (e.g., due to lack of compliance or to a pharmacokinetic interaction with another drug). In all situations, many of the interpretative problems in TDM can be minimized by a good knowledge of the various factors which affect the drug level-response relationship.

Factors affecting the drug level-response relationship

A throughout discussion of the factors responsible for the intra- and inter-patient variation in the drug level-response relationship is beyond the purpose of this article (for detailed information see refs. 1-5,9,14). Some of the most important examples will be reviewed briefly in this section.

Type and severity of the disease. It is well known that the serum drug levels required to obtain a desired pharmacological response is dependent upon the type and severity of the disease. The optimal serum concentration of a given antibiotic, for example, varies with the type of infecting organism and the site of the infection. Similarly, the optimal levels of various antiepileptic drugs vary depending on the form of epilepsy (7).

The duration of treatment. The concentration-response relationship may change with time. A good example is provided by barbiturates. Because of the development of functional tolerance, patients exposed chronically to phenobarbital may tolerate and indeed require serum drug levels which would be extremely toxic in

a naive subject (13).

Variation in drug binding to serum proteins. Although many drugs are extensively bound to serum proteins, only the free, non-protein bound fraction is available to cross the endothelial barrier and equilibrate with receptor sites in tissues. If the free fraction increases, the total drug concentration, which is the one usually measured for TDM purposes, may underestimate the concentration of free, pharmacologically active drug. Individual variation in drug-protein binding is one of the factors responsible for the inter-patient variability in response to a given serum drug concentration. An altered dose-response relationship can be observed in patients with abnormal protein binding: uremic patients, for example, may show a gross impairment in the protein binding of phenytoin and develop signs of toxicity at total serum phenytoin levels lower than usual (17). Concomitantly administered agents may displace protein-bound drugs from binding sites, resulting in an increased free fraction and a correspondingly altered dose-response relationship.

Presence of active metabolites. Several commonly monitored drugs, including procainamide, primidone, carbamazepine and some tricyclic antidepressants have active metabolites. Since patients may show differences in parent drug/metabolite ratios, it is not surprising that clinical response may not be consistently related to the levels of parent drug alone. We have found, for example, that patients receiving carbamazepine are likely to develop signs of toxicity when valpromide, the amide of valproic acid, is added to their treatment: this is explained entirely by a marked rise in the serum levels of the active metabolite carbamazepine-10,11-epoxide without any significant change in the levels of parent drug (Figure 3).

Pathophysiological factors leading to altered drug sensitivity. Physiological and pathological factors may affect drug sensitivity at receptor sites. Elderly subjects, for example, show increased sensitivity to benzodiazepines while hypokalemic patients are more vulnerable to digitalis toxicity (9).

Pharmacodynamic drug interactions. The dose-response curve to a given drug may be influenced by the simultaneous administration of other agents. An example is the progressive shift to the left of the concentration-effect relationship of theophylline at increasing concentrations of concurrently given terbutaline (19).

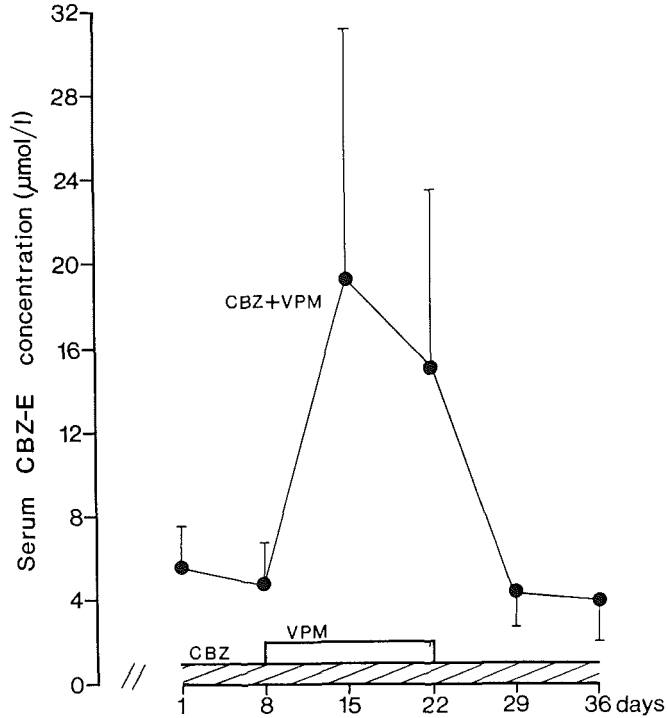


Figure 3. Effect of a 2-week treatment with valpromide (VPM), 900 mg/day, on the serum levels of carbamazepine-10,11-epoxide (CBZ-E) in patients stabilized on a fixed carbamazepine (CBZ) dosage. Data are means \pm s.d. in 6 patients. The slight decrease in carbamazepine-10,11-epoxide levels after 2 weeks on valpromide was related to a decrease in valpromide dosage in 2 patients who experienced adverse effects. Serum carbamazepine levels were not affected by the interaction. Modified from ref. 18.

Variation in drug assay. Intra- and inter-laboratory variation in drug assays is not a secondary cause of apparent inconsistencies between reported serum drug level results and concurrently assessed clinical response. The size and the implications of this problem have been stressed elsewhere (20).

THE DOSAGE-SERUM CONCENTRATION RELATIONSHIP

If TDM is to be used effectively, information about the expected relationship between serum level and response must be coupled with

knowledge about the effect that a given dosage adjustment will have on the serum level. In many cases, the relationship between dosage and serum level is linear and dose-independent, e.g. doubling the dose will also cause a doubling of the serum level at steady-state, at least within the therapeutically used dose range. In other cases, marked deviations from linearity may occur, and it is essential for the clinician to be aware of their existence.

Saturation kinetics

The enzymes responsible for the metabolism of several drugs may become saturated within the clinically occurring dose range. When saturation is approached, the drug metabolizing efficiency of the organism declines sharply, the rate of drug elimination becomes progressively slower and small dose increments can cause disproportionately large increases in serum drug concentration.

Among the commonly monitored drugs, phenytoin provides the most important example of saturation kinetics (21,22). As shown

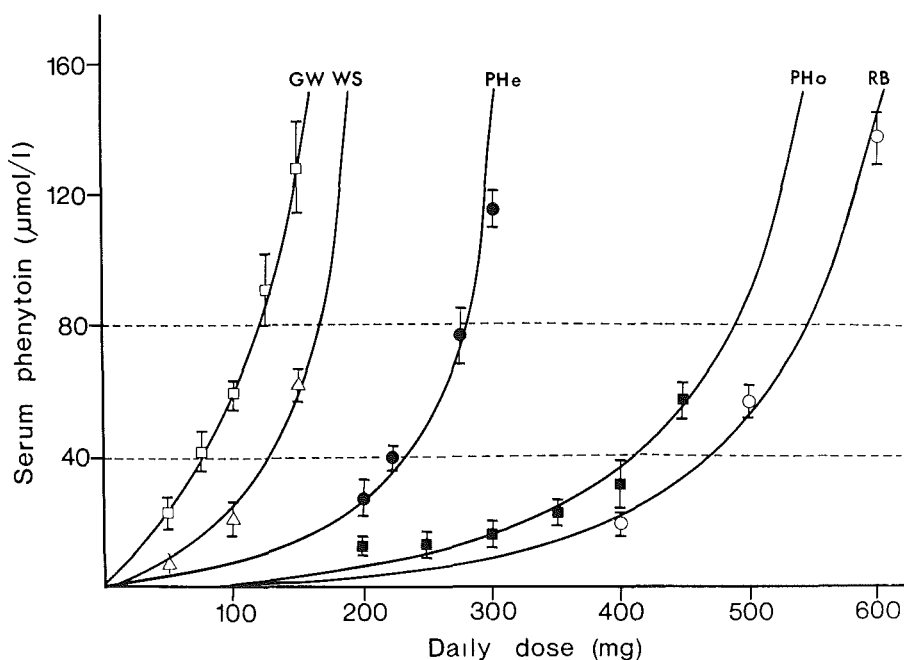


Figure 4. Relationship between steady-state serum phenytoin concentration and dose in 5 patients. Each point is the mean \pm s.d. of 3-8 separate measurements. The horizontal lines indicate the commonly quoted optimal concentration range. Modified from ref. 21.

in Figure 4, gradual occurrence of saturation of the enzymes responsible for phenytoin metabolism results in a curvilinear dose-serum level relationship. If the serum level is around 40 $\mu\text{mol/l}$ or greater, small changes in dose have a marked influence on the resulting serum drug level and, hence, magnitude of clinical response. Nomograms, graphical and computer-based methods have been designed to assist the clinician in deciding the phenytoin dosage change required to produce a desired serum concentration change (23,24). In most cases, however, clinical experience coupled with repeated serum level measurements is sufficient to make adequate dosage adjustments.

In addition to phenytoin, other drugs have been shown to exhibit saturation kinetics and a hyperbolic dose-serum level relationship. Examples among frequently monitored drugs include salicylic acid, theophylline and desipramine (25-27). At least in the case of theophylline, enzyme saturation within the therapeutic concentration range does not occur in all patients and has important consequences only in a limited number of cases.

Saturable protein binding

The binding of some drugs to plasma proteins is saturable, i.e. the unbound (free) fraction increases with increasing drug concentration within the clinically occurring serum concentration range. If the drug in question is a low-clearance compound which undergoes restrictive first-order elimination, the relationship between dosage and free serum drug concentration is linear whereas the relationship between dosage and serum concentration tends to flatten out. Under these conditions, any increase in total drug concentration will underestimate the increase in concentration of free, pharmacologically active drug and this should be taken into account when interpreting TDM results.

Typical examples of drugs exhibiting saturable binding include disopyramide (10) and valproic acid (28). In the case of valproic acid, saturation of binding to plasma proteins may occur simultaneously with saturation of metabolism and the dosage-serum concentration relationship may actually be rather complex (29). The occurrence of saturable binding makes a drug a good candidate for free level monitoring, but technical difficulties and

interpretative problems (30) restrict the applicability of this option.

Other sources of non-linear dose-level relationship

There is some evidence that when a given serum carbamazepine level is achieved, further increases in dosage result in disproportionately low increases in serum concentration (31). This phenomenon is not related to saturable plasma protein binding and may be due to decrease bioavailability at higher dosages or, alternatively, to dose-dependent autoinduction.

CONCLUSIONS

To use TDM effectively, the clinician must have a good knowledge of clinical pharmacology and be especially aware of the many factors which may influence the relationship between daily dose, resulting serum drug concentration and magnitude of pharmacological effect. As pointed out above, the interindividual variability in the dose-response relationship can be very large and it may not be controlled entirely by monitoring the serum concentration of the drug. Although TDM is a useful aid in the individualization of drug therapy, it is not a substitute for clinical observation and careful monitoring of drug response.

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Discussion - Dose-response relationships and therapeutic drug monitoring

L.F. Prescott

I wonder if you have any thoughts about how the dose response curve is modified by other drug therapy. Epileptic patients are sometimes prescribed drugs which are potential convulsants, such as mefenamic acid, antidepressants, or theophylline. Many other drugs in high doses will produce convulsions and epileptics are often prescribed these. Could you comment on that?

E. Perucca

The most common situation is that created by the prescription of several anticonvulsants. In that case the optimal concentration of a drug may be altered by the additional effect of a second drug. Sometimes, this is favourable and perhaps the best example is provided by valproic acid and ethosuximide, which exhibit synergistic effects, irrespective of their serum concentrations. More frequently, however, one does not increase much the efficacy but produces more toxicity, by adding a second drug. Some time ago we looked at a level/response relationship for carbamazepine in patients receiving this drug alone or in combination with phenobarbital and when the two drugs were combined, the threshold at which side effects of carbamazepine appeared was lower than when the drug was given alone. So the optimum ranges may change when a drug combination is used. As far as potentially convulsant drugs are concerned, that is a very complicated situation and I am not aware of studies looking specifically at the level/response relationship in such cases.

D.S. Davies

It has been said that probably doctors do not invest sufficient time and money to study two or possibly three dose levels of phenytoin in order to define the dose/plasma concentration curve in an individual while ample time and money is spent on the diagnosis. And yet, the dosage is critical and may be needed for a lifetime. I always find that rather odd.

E. Perucca

Yes, it is. On the other hand, when one has already studied a patient on three different dosages and serum levels at each of these dosages are available, it is easy to predict what effect a further dosage change will produce on the serum level.

D. Lalka

Many authors are critical of free level monitoring in a general population since for most drugs there is no convincing evidence that measuring free drug concentration is more useful than measuring total concentration. I think it is fair to say, however, that the animal data available are encouraging enough to justify continued exploration in this area.