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# DOSAGE REGIMEN DESIGN

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## 1. INTRODUCTION

Dosage regimen design is the selection of drug dosage, route, and frequency of administration in an informed manner to achieve therapeutic objectives. Deliberate planning of drug therapy is necessary because the administration of drugs usually involves risk of untoward effects. Specific drugs have inherently different risks associated with their use and a dosage regimen should be selected which will maximize safety. At the same time, the variability among patients in pharmacodynamic response demands individualized dosing to assure maximum efficacy.

Some factors which influence the selection of a dosage regimen include the dosage form of the drug, its pharmacokinetic characteristics, the patient's pathophysiology, and the patient's therapeutic needs. The suggested dosage regimens supplied with a drug product formulation are gradually improving in the use of pharmacokinetic principles and in providing allowances for individual patient needs. This article will review the general pharmacokinetic principles involved, the established methods, and some recent proposals for the design of drug dosage regimens.

### 1.1. PHARMACOLOGIC EFFECTS

Drugs are administered for their reversible or irreversible pharmacologic effects. Examples of the former type include the reduction of seizure activity from administration of anticonvulsants and the anesthesia produced by halothane. Irreversible effects occur following attenuated viral vaccine innoculation, ablative therapy in hyperthyroidism with $^{131}I$, and treatment of infectious diseases with antibiotics. With the early selection of an accurate dose and suitable method of administration, a pharmacologic response may indicate achievement of one or more therapeutic objectives. At other times, pharmacologic effects serve as feedback control in refinement of the dosage regimen. This process works best when the pharmacologic effects are direct and easily and accurately measureable, such as the reduction in heart rate caused by beta-adrenergic blockers or the increase in bleeding time from heparin administration. If the desired pharmacologic effects occur indirectly, then a longer time may elapse between a dosage change and appearance of the full intensity of the effect. An example is the delay in full anticoagulant effect which follows an adjustment in warfarin dosage.

When pharmacologic effects are not easily quantified, evaluation of efficacy may be especially difficult. During maintenance therapy of manic-depressive illness with lithium salts, a loss in efficacy may not be apparent for months following a reduction in dosage until recrudescence of symptoms occur. Similar examples occur with antiepileptic therapy.

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The safety component of appropriate drug therapy may be difficult to assess from pharmacologic effects alone. Prophylaxis of endocarditis may require administration of an aminoglycoside antibiotic for six weeks or longer. Evidence of efficacy may be present as sterile blood cultures, but the dosage regimen may allow insidious drug accumulation to occur which could lead to nephrotoxicity (Schentag *et al.*, 1977). In the evaluation of atrial fibrillation during digoxin therapy, either a loss of drug efficacy or a toxic drug effect might be present. Here, a serum drug concentration measurement might be diagnostic. The most effective and realistic method for assuring safe and efficacious drug therapy is an integrated approach using both pharmacologic effects and serum drug concentrations to serve as feedback control in refinement of the dosage regimen.

### 1.2. SERUM DRUG CONCENTRATIONS

When either a minimum or threshold concentration has an established relationship with a pharmacologic effect or when an upper concentration boundary is associated with decreased efficacy or with toxicity, serum drug concentrations become relevant markers of appropriate therapy. A practical example of this concept is the threshold concentration that exists for antimicrobial therapy where *in vitro* testing of a patient's infecting organism with serial dilutions of an antibiotic can be used to determine the effective minimum inhibitory concentration (MIC) (Tallarida and Jacob, 1979). An alternative to individual MIC determinations is large scale testing using different strains of the same pathogen to determine MIC's for several antibiotics. Data derived from these types of studies are useful to design a dosage regimen wherein the MIC is exceeded during each dosage interval.

A minimum effective concentration (MEC) can be established for many drug classes. The usual procedure is to construct dose–response curves in relation to plasma concentration and to identify the concentration below which 20% of the study population fails to exhibit the measured pharmacologic response as the MEC. The upper limit to the 'therapeutic range' is established as either the concentration below which 80–85% of the study population responds, or response is limited by intervening toxicity. This concept is illustrated in Fig. 1. The therapeutic concentration range may be determined by prospective clinical trial, as was done for theophylline (Mitenko and Ogilvie, 1973; Weinberger and Bronsky, 1974) or by retrospective data examination, as was done with the antimanic effect of lithium (for review, see Amdisen, 1978). The ratio of the upper to lower concentration boundary has been termed the 'therapeutic index' (TI) and is a useful concept in dosage regimen design. An additional term, 'therapeutic window', has been applied to drugs with a therapeutic range above which toxicity does not necessarily intervene but

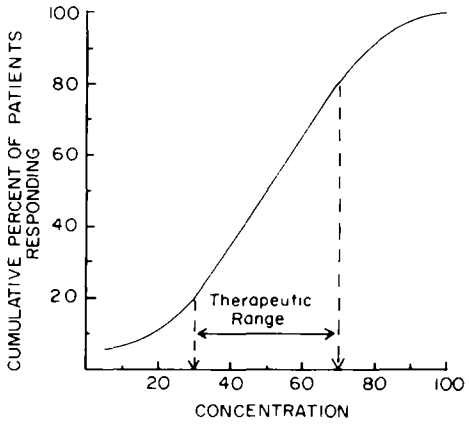


FIG. 1. The cumulative per cent response, or dose response curve. For many drugs the characteristic shape of the cumulative curve is seen when the abscissa is expressed as log concentration rather than concentration. A 'therapeutic range' may be established wherein 20–80% of the patient population shows the desired pharmacologic response without intervening toxicity.

the desired pharmacologic response appears less likely to occur. An example is the 150 ng/ml steady-state concentration of nortriptyline above which spontaneous remission of depression may be inhibited (Kragh-Sorensen *et al.*, 1976).

A serum concentration within a reported therapeutic range provides evidence that the drug dosage regimen employed should be appropriate for patients with characteristics similar to the study population in which the range was determined. Therapeutic ranges have been reported for numerous drugs, but these data usually reflect the results of a limited selection of patients and may not apply to a specific individual. In utilizing data of this nature, one should critically examine the characteristics of the patients studied and the details of the dosage regimen used to establish the particular range. This latter fact can be important because sampling time differences among studies can lead to different conclusions. A common caveat is that serum drug measurements must be interpreted in the context of the patient's therapeutic needs and clinical response to the drug.

## 2. THEORETICAL PRINCIPLES

Mathematical models to describe the sojourn of drug and metabolites in the body are becoming increasingly sophisticated. An impediment to progress in clinical pharmacokinetics is obtaining biological samples to confirm these models. Nevertheless, a mathematical basis for serum concentration predictions has practical utility. The advantage of theoretical insight is that it enables us to evaluate experimental data critically, to determine the relative meaning of unexpected results, and in general, to reduce the amount of uncertainty that lies in applying empiric observations to the pragmatic task of dosage regimen design.

### 2.1. Linear Drug Disposition

When the rate of drug elimination from the body at any time is proportional to the amount of drug in the body at that time, a first-order or linear process is operative. Invoking the assumption of linearity also means that a drug undergoes each kinetic process in the body, e.g. distribution across membranes or binding to tissue proteins, without appreciably disturbing that process. Linearity for any drug occurs only over a finite concentration range, and any dose producing concentrations within the linear range will follow the same fate in the body as another. Many clinically useful drugs produce their desired pharmacologic response without exceeding a concentration range associated with linearity.

#### 2.1.1. *Single Doses*

The blood (serum or plasma) concentration–time profile following single doses of many therapeutically useful drugs resembles that shown in Fig. 2. Drug concentration, $C$, at any time, $t$, can be described by a polyexponential equation generally consisting of four terms or less

$$C = \sum_{i=1}^{n} C_i \cdot e^{-\lambda_i(t)} \tag{1}$$

where $C_i$ is the hybrid coefficient associated with the $i$th exponent. The $\lambda_i$ and $C_i$ values represent the slopes ($S$) and heights ($H$), respectively, of the concentration–time curve and can be determined by linear regression analysis using manual (Riggs, 1963; Gibaldi and Perrier 1975) or computer fitting techniques (Daniel and Wood, 1980) without recourse to any particular pharmacokinetic model (see also Metzler, 1981). Along with the area under the curve ($A$, AUC) and the area of the first moment curve ($M$, AUMC), they constitute the SHAM properties of an observed kinetic process (Caprani *et al.*, 1975). These properties can be used to either calculate rate constants associated with a variety of models or to calculate model-independent parameters (Wagner, 1976).

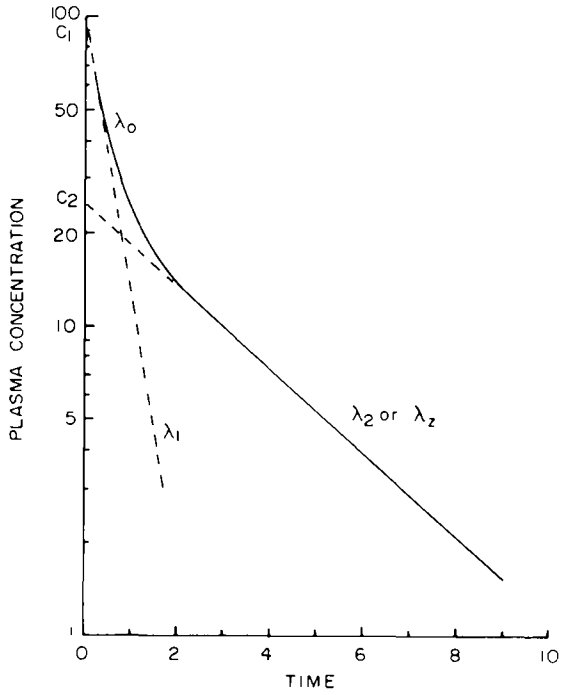


FIG. 2. Log linear intravenous drug disposition curve showing the biexponential decline in concentration as a function of time. The slopes ($\lambda_0$, $\lambda_1$, $\lambda_2$, or $\lambda_z$) and Heights ($C_1$ and $C_2$) are part of the SHAM properties of the curve.

Following a bolus intravenous dose ($D$), several model independent parameters can be determined to enhance the ability to individualize dosage regimens. The volume of the central distribution space ($V_1$) (Riegelman *et al.*, 1968) is calculated from

$$V_1 = D/H_0 = D/\Sigma C_i \tag{2}$$

where $H_0$ is the sum of the heights or zero time intercepts. The volume of distribution at steady-state ($V_{ss}$) (Benet and Galleazzi, 1979) can be calculated from

$$V_{ss} = D(\text{AUMC}/\text{AUC}^2). \tag{3}$$

Equation (3) applies only to single dose administration when drug input is by a non-first-pass route and clearance occurs from the central compartment of a mamillary model. If an intravenous infusion is administered a correction must be made for the infusion time, $t_{inf}$

$$V_{ss} = \frac{D \cdot \text{AUMC}}{(\text{AUC})^2} - \frac{D \cdot t_{inf}}{2(\text{AUC})}. \tag{4}$$

The total plasma clearance ($CL$) (Rowland *et al.*, 1973) from

$$CL = \frac{D}{\text{AUC}} \tag{5}$$

can be calculated for parenteral input. The total clearance is equal to the sum of all organ clearance processes

$$CL = CL_H + CL_R + CL_{other} \tag{6}$$

where $CL_H$ is the hepatic clearance and $CL_R$, the renal clearance. If the bioavailability, $F$, is known, the apparent oral clearance ($CL_{po}$) following an oral dose, $D_{po}$, (Wilkinson and Shand, 1975) is

$$CL_{po} = F \cdot D_{po}/\text{AUC}. \tag{7}$$

The above parameters have limited applicability in the selection of single doses since serum drug concentrations can be measured only after drug therapy has been initiated. However, if the volume of distribution is known or a reasonable estimate available ($V_{ss}$), then the dose required to achieve a target concentration, $C(o)$, can be calculated

$$\text{Dose} = V_{ss} \cdot C(o). \tag{8}$$

This relationship is useful when drug disposition is lengthy so that a single dose produces a sustained concentration within the presumed therapeutic range to achieve the treatment objectives. This situation may occur when clearance depends predominately upon an organ currently in a nonfunctioning state (Eqn 6) and is illustrated by the use of aminoglycoside antibiotics in severe renal failure. Here a single dose may provide tissue concentrations above the MIC for much or all of the required period of therapy.

Equation (8) is useful to calculate the dose to attain the serum concentration that would result if drug input and distribution were instantaneous. However, a transient peak concentration higher than expected may occur when calculated intravenous doses are administered due to the time necessary for mixing and distribution. If used for oral doses, Eqn (8) will likely under-estimate the required dose to achieve a target concentration, especially if bioavailability is less than complete.

### 2.1.2. *Multiple Bolus Doses*

The assumption of linearity implies that drug inputs are superimposible, i.e. a direct proportionality exists between drug concentration at any time and the size of the dose. It is upon this principle of superposition that calculations involving multiple doses are possible. Additional assumptions are an equal dose administration at a constant interval and the condition that no time dependent changes in pharmacokinetics occur.

Bolus doses are usually administered as either multiple dose intravenous therapy or oral doses. Equation (1) can be converted to describe $C$ after $N$ number of bolus doses by any route of administration

$$C = \sum_{i=1}^{n} C_i \left( \frac{1 - e^{-N\lambda_i \tau}}{1 - e^{-\lambda_i \tau}} \right) e^{-\lambda_i t} \tag{9}$$

where $t$ is the time lapse since the last dose, $\tau$ is the dosage interval, and the parenthetical term represents the multiple dosing function developed by Dost (1953).

At steady-state, when an infinite number of doses have been given, Eqn (9) reduces to

$$C_{ss} = \sum_{i=1}^{n} C_i \left( \frac{1}{1 - e^{-\lambda_i \tau}} \right) e^{-\lambda_i t} \tag{10}$$

where $C_{ss}$ is the concentration of drug within a dosing interval at steady state.

Assuming that each dose in a multiple dosing regimen is administered in the post-absorptive, post-distributive phase of the preceeding dose, all exponential terms approach zero in Eqn (10) except for the $\lambda_z$ term. Letting $\tau$ equal the end of the dosage interval, the quotient of Eqns (10) and (1) indicates the degree of drug accumulation between the first dose and steady-state, the accumulation ratio, $r$

$$r = \frac{C_{\min(ss)}}{C_{\min(1)}} = \frac{1}{1 - e^{-\lambda_z}} \cdot \tau \tag{11}$$

where $C_{\min(1)}$ and $C_{\min(ss)}$ are the minimum plasma drug concentrations following the first dose and at steady-state, respectively. Equation (11) reveals that $\lambda_z$ and $\tau$ are the most important factors controlling the accumulation of drugs and they can be assessed with the first dose. The accumulation ratio, $r$, is a nonlinear function of $\lambda_z$ and $\tau$ but can be used, as explained below, in dosage selection.

Design of multiple dosing regimens is facilitated by knowledge of $\lambda_z$ as it allows a calculation of the time for $C$ to decline to any proportion of an initial concentration or

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