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THE SCIENCE OF DOSAGE FORM DESIGN

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Dosage regimens

Stuart Proudfoot (updated by John Collett)

CHAPTER CONTENTS

Dosage regimens: their influence on the concentration–time profile of a drug in the body 275

One-compartment open model of drug disposition in the body 276
Rate of drug input versus rate of drug output 276
Elimination rate constant and biological half-life of a drug 277
Concentration–time curve of a drug in the body following the peroral administration of equal doses of a drug at fixed intervals of time 278

Important factors influencing steady-state plasma drug concentrations 281
Dose size and frequency of administration 281
Size of dose 281
Interval between successive equal doses 281
Summary of the effects of dose size and frequency of administration 282
The concept of 'loading doses' 284
Influence of changes in the apparent elimination rate constant of a drug: the problem of patients with renal impairment 285
Influence of the 'overnight no-dose period' 286
Concluding comments 287

Bibliography 288

DOSAGE REGIMENS: THEIR INFLUENCE ON THE CONCENTRATION–TIME PROFILE OF A DRUG IN THE BODY

The subject of dosage regimens is concerned with the dose, time of administration and drug plasma levels factors associated with ***multiple*** dosing of a drug. The influence that physiological factors, the physicochemical properties of a drug and dosage form factors can have in determining whether a therapeutically effective concentration of a drug is achieved in the plasma following peroral administration of a ***single*** dose of drug has been discussed previously in Chapters 16, 17 and 18.

Some drugs, such as hypnotics, analgesics and antiemetics, may provide effective treatment following the administration of a single dose. However, the duration of most illnesses is longer than the therapeutic effect produced by the administration of a single dose of a drug in a conventional dosage form, i.e. a dosage form which is formulated to give rapid and complete drug release. In such cases doses are usually administered on a repetitive basis over a period of time determined by the nature of the illness. For instance, one 250 mg ampicillin capsule may be administered every 6 hours for a period of 5 days to treat a bacterial infection. Such a regimen, in which the total dose of drug (i.e. in this example 5 g) administered over 5 days is given in the form of multiple doses (i.e. each of 250 mg) at given intervals of time (i.e. every 6 hours) is known as a ***multiple-dosage regimen***.

The proper selection of both the dose size and the frequency of administration is an important factor that influences whether a satisfactory therapeutic plasma concentration is achieved and maintained over the prescribed course of treatment. Thus the design of a multiple-dosage regimen is crucial to successful drug therapy.

ONE-COMPARTMENT OPEN MODEL OF DRUG DISPOSITION IN THE BODY

In order to understand how the design of a dosage regimen can influence the time course of a drug in the body, as measured by its plasma concentration–time curve, consider that the complex kinetic processes of drug input, output and distribution in the body may be represented by the pharmacokinetic model of drug disposition, the one-compartment open model, shown in Figure 19.1. In this case the drug is considered to be distributed instantly throughout the whole body following its release and absorption from the dosage form. Thus the body behaves as a single compartment in which absorbed drug is distributed so rapidly that a concentration equilibrium exists at any given time between the plasma, other body fluids, and the tissues into which the drug has become distributed.

To assume that the body behaves as one-compartment open model does not necessarily mean that the drug concentrations in all body tissues at any given time are equal. The model does assume, however, that any changes that occur in the plasma reflect quantitatively changes occurring in the concentration of drug at the site(s) of action.

Rate of drug input versus rate of drug output

In a one-compartment open model, the overall kinetic processes of drug input and drug output are described by first-order kinetics. In the case of a perorally administered dosage form, the process of drug input into the body compartment involves drug release from the dosage form and passage of the drug across the cellular membranes constituting the gastrointestinal barrier. The rate of input or absorption represents the net result of all these processes. The rate of input (absorption) at any given time is proportional to the concentration of drug, which is assumed to be in an absorbable form, in solution in the gastrointestinal fluids at the site(s) of absorption, i.e. the effective concentration, C_e, of drug at time t. Hence:

$$\text{rate of drug input at time } t \propto C_e \qquad (19.1)$$

and

$$\text{rate of drug input at time } t = -k_a C_e \qquad (19.2)$$

where k_a is the apparent absorption rate constant.

The negative sign in Eqn 19.2 indicates that the effective concentration of drug at the absorption site(s) decreases with time. The apparent absorption rate constant gives the proportion (or fraction) of drug that enters the body compartment per unit time. Its units are time^{-1}, e.g. h^{-1}.

Unlike the rate of drug input into the body compartment, the apparent absorption rate constant, k_a, is independent of the effective concentration of drug at the absorption site(s). Because the rate of drug input is proportional to the effective drug concentration, it will be maximal following the administration of a dose contained in a peroral dosage form which gives rapid and complete drug release. The rate of drug input will decrease gradually with time as a consequence of the effective drug concentration at the absorption site(s) decreasing progressively with time, chiefly as a result of absorption into the body compartment. Other processes, such as chemical degradation and movement of drug away from the absorption site(s), will also contribute to the gradual decrease in the effective drug concentration with time.

In the case of a one-compartment open model, the rate of drug output or elimination is a first-order process. Consequently, the magnitude of this parameter at any given time is dependent on the concentration of drug in the body compartment at that time. Immediately following administration of the first dose of a peroral dosage form, the rate of drug output from the body will be low as little of the drug will have been absorbed into the body compartment. However, as absorption proceeds – initially at a higher rate than the rate of drug output – the net concentration of drug in the body will increase with time. Likewise, the rate of drug output from the

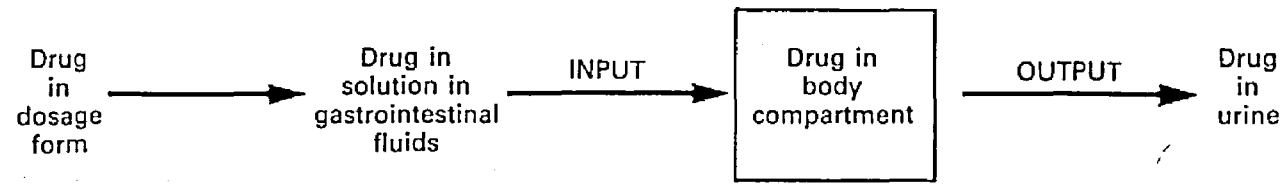


Fig. 19.1 One-compartment open model of drug disposition for a perorally administered drug.

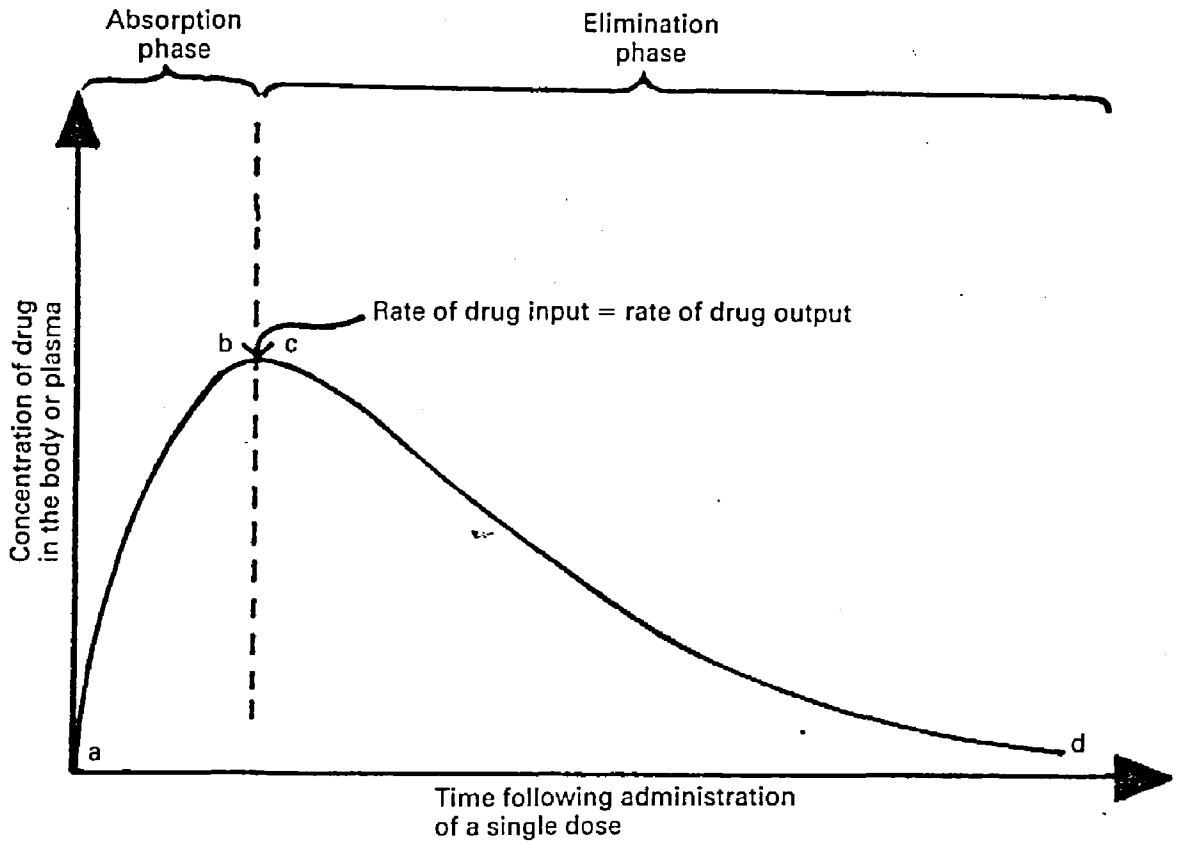
body compartment will also increase with time. As the rate of drug output is increasing with time while the rate of input into the body compartment is decreasing with time, the situation is eventually reached when the rate of drug output just exceeds that of drug input. Consequently, the net concentration of drug in the body compartment will reach a peak value and then begin to fall with time. The ensuing decreases in the net concentration of drug in the body will also cause the rate of drug output to decrease with time.

These changes in the rates of drug input and output relative to each other with time are responsible for the characteristic shape of the concentration–time course of a drug in the body shown in Figure 19.2 following peroral administration of a single dose of drug.

It is evident from the above discussion and Figure 19.2, that the greater the rate of drug input relative to that of drug output from the body compartment over the net absorption phase, the higher will be the peak concentration achieved in the body or plasma following peroral administration of a single dose of drug. This interplay explains why increases in dose size and formulation changes in dosage forms which produce increases in the effective concentration of drug at the absorption site(s), result in higher peak plasma and body concentrations being obtained for a given drug. It should also be noted that any unexpected decrease in the rate of drug output relative to that of drug input, which may occur as the result of renal impairment, is also likely to result in higher plasma and body concentrations of drug than expected, and the possibility of the patient exhibiting undesirable side-effects. The adjustment of dosage regimens in cases of patients having severe renal impairment is considered later in this chapter.

Elimination rate constant and biological half-life of a drug

In the case of a one-compartment open model the rate of elimination or output of a drug from the body compartment follows first-order kinetics (Chapter 7) and is related to the concentration of drug, C_t,



a–b rate of drug absorption > rate of drug elimination
c–d rate of drug elimination > rate of drug absorption

Fig. 19.2 Concentration–time course of a drug in the body following peroral administration of a single dose of drug which confers one-compartment open model characteristics on the body.

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