AN INTRODUCTION TO PHARMACOKINETICS

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PREFACE

This book was prompted when one of us had to give a series of lectures to medical students on the subject of pharmacokinetics. These lectures needed to start with the very basics of the subject. However, no simple introduction appeared to have been published to help either lecturer or student! Convinced that the essentials of pharmacokinetics could be understood without a profound knowledge of mathematics, we wrote the following text. Please remember that this is a simple introduction to what can be a very complex, although interesting, subject. Nevertheless, we believe that the simple basic concepts presented here will attract you as they have captivated us. We do not claim to be experts in pharmacokinetics but we do find ourselves using the concepts in this book almost daily in our work.

The text will be of use to students of pharmacy, pharmacology, human or veterinary medicine, toxicology and drug metabolism. It will also be useful background reading for others involved in the development and use of drugs. Sixth-form students of biology should not find the text too difficult and may find it of interest.

The text is presented in a special format since the mathematical treatment is restricted as far as possible to self-contained boxes. We suggest that you ignore these boxes on the first reading of the text. A second reading should, however, include the mathematical treatment. The material in the boxes can also be read and understood independently. Since this is an introductory text, some of the more complex concepts and mathematics are not included.

You will find it of great benefit to work through the examples given at the end of the book since these illustrate the main concepts discussed in the text.

B.C.
D.A.S.

CONTENTS

INTRODUCTION

The *pharmacokineticist* seeks to understand more about how drugs act and behave, and to predict what they will do in new situations. The medical sciences owe much to the development of this relatively young discipline, *pharmacokinetics*.

Pharmacokineticists use words, symbols and mathematical equations to express and predict drug behaviour.

WORDS *describe what happens*. The concepts of pharmacokinetics can be explained in words. A profound understanding of mathematics is not necessary to grasp these principles.

SYMBOLS *are used with defined meanings*. There is considersiderable confusion about the symbols used in publications on pharmacokinetics and for this reason the symbols used here are defined wherever necessary.

The MATHEMATICAL EQUATIONS *used are functions* and show the relationships between one variable and another. The symbols and mathematics which form the language of pharmacokinetics are contained in boxes within the text of this book.

The subject of *kinetics* is concerned with the relationships between the motions of bodies and the forces acting upon them. Pharmacokinetics is therefore the science of the relationships between the movement of a drug through the body and the processes affecting it (i.e. the forces acting upon it). It is a discipline which describes the *time*-course of the movement of a drug into, around and out of the body.

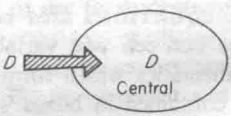
INTO *the body*. Most drugs need to be transported to their site of action by the blood. For the drug to be present in the blood following extravascular administration it needs to be *absorbed*. Absorption must therefore have taken place before a drug appears in the circulation after administration at an extravascular site. Drugs administered intramuscularly, intraperitoneally, topically, orally, or *per rectum* need to be absorbed in order to appear in the circulation. Drugs administered intravenously and intra-arterially do not.

AROUND *the body*. Since the target organ or site is not usually the blood, the drug, once it is present in the circulation,

must penetrate tissues in order to act. Drugs are not usually specific for a particular tissue and therefore will reach a number of tissues and organs. The drug can be said to be undergoing *distribution* when it is present in the blood and is penetrating organs and tissues.

OUT OF *the body*. *Elimination* is the removal of drug from the body and may be by renal and biliary excretion of the unchanged drug molecule or by metabolism. Two organs particularly important for eliminating drugs are the liver and the kidneys. With a few types of drugs other routes of elimination may assume importance, for example, in the case of volatile anaesthetics eliminated via the lungs.

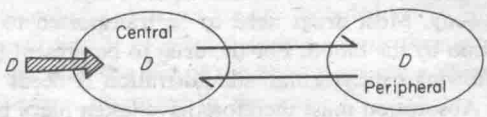
Into



The drug (*D*) is absorbed into the central compartment from its site of administration.

(The central compartment is often equated with the blood but, in fact, it includes all those tissues and organs with which the drug is in rapid equilibrium.)

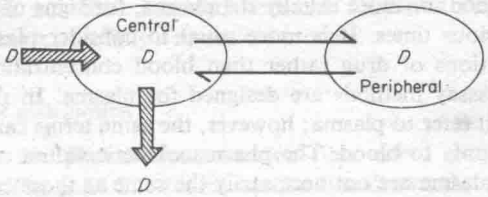
Around



D distributes to peripheral compartment(s) in a reversible manner ($\rightleftharpoons$).

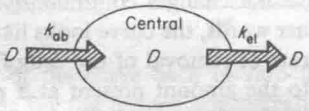
(The peripheral compartments are often equated with the tissues but, in pharmacokinetic terms, could include any areas in the body with which the drug equilibrates relatively slowly.)

Out



D is removed irreversibly ($\rightarrow$) from the central compartment, that is, it is excreted or metabolized.

N.B. The above symbols represent a simple two-compartment model for the absorption, distribution and elimination of drugs. We will return to the concept of compartments later. In the mathematical treatment of most of the problems which follow we will use a simple one-compartment model, i.e.



Where k_{ab} and k_{el} are constants which characterize the rate of movement of D.

In this model, all the tissues and organs to which D penetrates, behave as though they were in ready equilibrium with the blood.

RAPID (BOLUS) INTRAVENOUS INJECTION

To study the mathematical equations which describe the above processes (movements *into*, *around* and *out* of the body) we must start with the simplest example. If we give someone a rapid intravenous injection (termed a bolus) of a drug, we introduce the drug directly into the blood and therefore we are, in effect, studying only the distribution and elimination. If the drug we have administered is very rapidly distributed, we have simplified the system even further so that we are, in fact, studying only elimination. We can sample

the blood, or more usually the plasma, for signs of the drug at various times. It is more usual to consider plasma concentrations of drug rather than blood concentrations since most assay methods are designed for plasma. In this book we will refer to plasma; however, the same terms can equally well apply to blood. The pharmacokinetic values calculated from plasma are not necessarily the same as those calculated from whole blood.

If we plot the results of our plasma concentration determinations against time, we will usually find that the concentration declines rapidly at first and then more and more slowly. If the method of analysis is sensitive enough, the rate of decline would eventually appear almost to stop. In practical terms, however, this represents such a minute quantity of the drug that it does not usually matter.

A relationship like this shows that the *rate* of removal of drug from the plasma changes continuously (in this case it decreases). In other words, the curve looks like an *exponential* decline and the rate of removal of the drug from the plasma is proportional to the amount present at a given time. This can be likened to the drug exerting a kind of 'pressure' to drive itself out: as the concentration of drug drops, so the 'pressure' decreases. Another way of describing this process is to say that a constant fraction of the drug present at any time is eliminated in unit time. This may be expressed as k_{el}, the elimination rate constant.

At first sight it is not easy to see why the removal of a drug from the plasma should take this form. In order to understand it, we must consider briefly the processes which contribute to the decline of drug in plasma. These are:

1 uptake by the liver and subsequent elimination in the bile,
2 elimination in the urine by glomerular filtration,
3 elimination in the urine by tubular secretion,
4 metabolism.

You may recognize that each of these processes is essentially one way (i.e. not reversible). Thus, drug is removed from the plasma and is not replaced. Furthermore, the rates at which these processes occur are proportional to the drug concentration driving them. Therefore, elimination from the plasma appears to be exponential. Uptake into the

tissues has not been included with the routes of removal because this is normally a reversible process.

Volume of distribution

Consider the plasma concentration–time curve shown in Figure 1. The solid line represents the line drawn through a series of plasma concentration determinations.

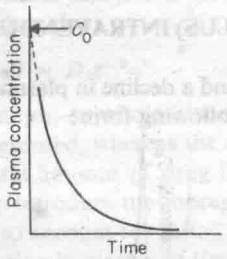


Figure 1

Extrapolation of the curve back to zero time would give an apparent value for the plasma concentration at zero time (C_0). It is evident that the total amount of drug in the body at zero time is given by this concentration multiplied by the volume in which the drug is distributed, assuming even distribution. This is the *volume of distribution*. The total amount of drug in the body at zero time in the case of a rapid intravenous dose is equal to the dose injected. Therefore, we can easily calculate this volume of distribution.

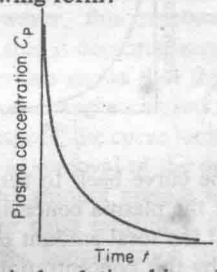
In practice, the extrapolation back to zero time is carried out much more conveniently using a $\log_{10}$ plasma concentration versus time curve as outlined on page 6.

It should be appreciated that this volume of distribution is an *apparent volume*, i.e. it does not necessarily reflect a literal volume of fluid in which the drug is dissolved. It includes, for example, tissues in which the drug, although in equilibrium with plasma, may be more highly concentrated than in the plasma. This explains why the reported volume of distribution often exceeds the total volume of the body. Nevertheless, the volume of distribution of a drug often yields interesting information and it is related to several other parameters such as clearance.

A small volume of distribution (e.g. less than 5 litres in man) implies that the drug is largely retained within the vascular compartment. Distribution within the extracellular fluid would yield a volume of distribution of approximately 15 litres. Large volumes of distribution imply distribution throughout the total body water or concentration in certain tissues.

RAPID (BOLUS) INTRAVENOUS INJECTION

We usually find a decline in plasma concentration with time of the following form:



The mathematical relationship which appears to describe the above relationship fairly closely is of the general form:

$$X = X_0 e^{-kv}$$

i.e. X at any given value of y is an exponential function of the starting value X_0 at $y=0$.

It is a simple step to convert this equation for application to drugs:

$$D = D_0 e^{-k_{el}t}$$

where: D is the amount of drug in the body at time t;
D_0 is the initial amount of drug;
k_{el} is a constant which describes the rate of removal (elimination) of drug from the body (*the elimination rate constant*).

Thus, the rate of elimination of the drug varies continuously depending upon its concentration at any given

time, i.e.

$$\frac{dD}{dt} \propto D$$

and therefore

$$\frac{dD}{dt} = -k_{el}D$$

The negative sign indicates that D decreases with time. This can be integrated to give:

$$D = D_0 e^{-k_{el}t}$$

Usually, a plasma, serum, or whole blood concentration of the drug is measured, whereas the above equation describes the total amount of drug in the body. Therefore, we need to introduce the concept of volume of distribution (V_D) to account for this.

If C_{P_t} = concentration in plasma at time t, then the total amount of drug in the body at time t is given by:

$$D = C_{P_t}V_D$$

where V_D is the *apparent* volume of distribution or for any value of time t

$$C_P = \frac{D_0}{V_D} e^{-k_{el}t}$$

or

$$C_P = C_0 e^{-k_{el}t}$$

C_0 is the theoretical initial plasma concentration at time t_0 after a bolus i.v. dose.

Log_{10} plasma concentration versus time

Because the decline in plasma concentration behaves exponentially, it is usual to plot the results semi-logarithmically to obtain a straight line (Figure 2). The use of semi-logarith-

mic paper allows the plasma concentration to be plotted directly without using $\log_{10}$ tables.

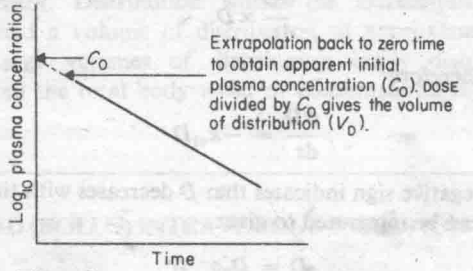


Figure 2

By obtaining a linear plot we are able to extrapolate easily the straight line back to obtain the concentration of drug in plasma at time zero. This theoretical concentration is not measurable by sampling since mixing of the drug is not instantaneous. We are also governed in the obtainment of samples by ethical and practical constraints. Drugs are not administered to patients solely for the purpose of carrying out pharmacokinetics.

Log $_{10}$ plasma concentration versus time

$$C_P = C_0 e^{-k_{el}t}$$

can be written

$$\ln C_P = \ln C_0 - k_{el}t$$

or

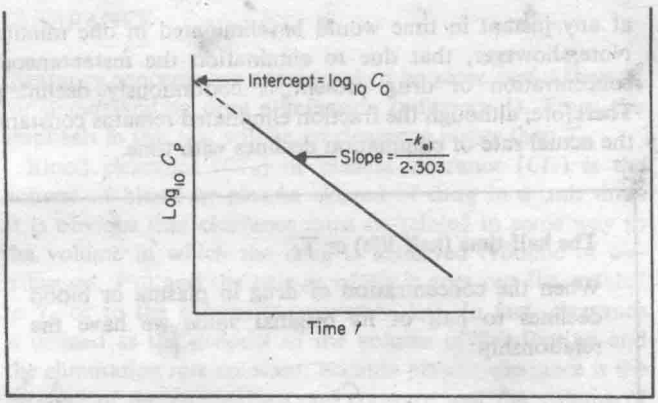
$$\log_{10} C_P = \log_{10} C_0 - \frac{k_{el}t}{2{\cdot}303}$$

Therefore, a plot of $\log_{10}$ against time is linear with a slope of:

$$\frac{-k_{el}}{2{\cdot}303}$$

and intercept when $t = 0$ is given by:

$$\log_{10} C_0$$



The half-time (half-life) or $T_{\frac{1}{2}}$

The half-time ($T_{\frac{1}{2}}$) is the time taken for the concentration of drug in the blood or plasma to decline to half of its original value.

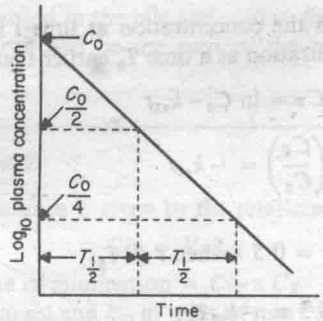


Figure 3

If the $\log_{10} C_P$ versus time plot is linear (Figure 3), then $T_{\frac{1}{2}}$ will be the same over the entire time period.

The elimination rate constant (k_{el}) is a constant which is more useful to the pharmacokineticist and it can be obtained by simple calculation from $T_{\frac{1}{2}}$. It is a proportionality constant, and may be defined as the fraction of drug present at any time which would be eliminated in unit time. For example, if k_{el} is 0·1 min^{-1}, 10 per cent of the drug present

at any instant in time would be eliminated in one minute. Note, however, that due to elimination the instantaneous concentration of drug present is continuously declining. Therefore, although the fraction eliminated remains constant, the actual rate of elimination declines with time.

The half-time (half-life) or $T_{\frac{1}{2}}$

When the concentration of drug in plasma or blood declines to half of its original value we have the relationship:

$$\frac{C_P}{C_0} = 0{\cdot}5$$

or, more generally, in the case of a linear $\log_{10} C_P$ versus t plot:

$$\frac{C_{P_t}}{C_{(t-T_{\frac{1}{2}})}} = 0{\cdot}5$$

where C_{P_t} is the concentration at time t and $C_{(t-T_{\frac{1}{2}})}$ is the concentration at a time $T_{\frac{1}{2}}$ earlier than t.

Since $\ln C_P = \ln C_0 - k_{el}t$

i.e. $\ln\left(\frac{C_P}{C_0}\right) = -k_{el}t$

and $\frac{C_P}{C_0} = 0{\cdot}5$ when $t = T_{\frac{1}{2}}$

then $\ln 0{\cdot}5 \equiv -k_{el}T_{\frac{1}{2}}$

since $\ln 0{\cdot}5 = 0{\cdot}693$

$$T_{\frac{1}{2}} = \frac{0{\cdot}693}{k_{el}}$$

From a linear $\log_{10} C_P$ versus t plot we can obtain $T_{\frac{1}{2}}$ and therefore the elimination rate constant (k_{el}). k_{el} has the dimensions of h^{-1}, min^{-1}, or s^{-1} depending on whether $T_{\frac{1}{2}}$ is in hours, minutes or seconds respectively.

CLEARANCE

Clearance concepts are considered to be more useful than $T_{\frac{1}{2}}$ for understanding drug elimination (reference 1). Thus, the emphasis in this text will be on clearance rather than $T_{\frac{1}{2}}$.

Blood clearance (Cl_B) or plasma clearance (Cl_P) is the volume of blood or plasma cleared of drug in a unit time. It is obvious that clearance must be related in some way to the volume in which the drug is dissolved (volume of distribution, V_D) and the *rate* at which it goes out (i.e. related to $T_{\frac{1}{2}}$ or to the elimination constant k_{el}). In fact, clearance is defined as the product of the volume of distribution and the elimination rate constant. Because plasma clearance is the product of the elimination rate constant and the volume of distribution, we would expect it to be closely related to the size or area of the plasma plot. Appendix 1 illustrates the concept of clearance.

If a drug is cleared from the plasma by several processes then the total clearance is the sum of the individual clearances. For example, if a drug is cleared from the plasma by being excreted unchanged in the bile and also in the urine, then the plasma clearance will be the sum of the biliary and renal clearances.

CLEARANCE

Plasma clearance is given by the relationship

$$Cl_P = V_D k_{el}$$

and the rate of elimination $= Cl_P \times C_P$

If V_D is in ml and k_{el} in units of min^{-1}, then Cl_P has the dimension ml min^{-1}.

Clearance is the sum of individual clearance values. For example, plasma clearance (Cl_P) is the sum of metabolic clearance (Cl_M) and renal clearance (Cl_R) for a drug cleared by metabolism and renal excretion:

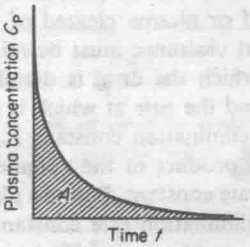
$$Cl_P = Cl_M + Cl_R.$$

A similar equation could be written for blood clearance. Or similarly, hepatic clearance could be the sum of clearance by metabolism and biliary clearance:

$$Cl_H = Cl_{BILE} + Cl_M$$

The area (A) shown in the figure below is described as the area under the curve or AUC. Mathematically,

$$AUC_{0-\infty} = \int_0^\infty C_P \, dt.$$



For intravenous bolus injection the clearance can be calculated from the relationship :

$$Cl_P = \frac{DOSE}{AUC}$$

Similarly blood clearance can be calculated from blood concentration data or from plasma data by knowing the partitioning of the drug between plasma and red cells over the range of concentrations measured.

The relationship between clearance, DOSE and AUC is true whatever the route of drug administration. For routes other than intravascular, however, DOSE is equated with the fraction of the administered dose which is actually absorbed.

This relationship is particularly useful since clearance is independent of the type of pharmacokinetic model used. We will understand more of the pharmacokinetic model when we consider models with more than one compartment later.

AREA UNDER THE CURVE (AUC)

For a pharmacological response to occur in an organ or tissue different from the site of absorption, drug has to be