A TEXTBOOK OF CLINICAL PHARMACOLOGY

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PREFACE

The last thirty years have seen an unprecedented increase in the number and in the range of activity of drugs used in the treatment of human disease. Although their use goes back far into antiquity, it has only been relatively recently that mythology and empiricism have given way to systematic and scientific study. In parallel with the drug explosion, clinical pharmacology has emerged as a distinct discipline, one of the chief reasons for this being the realisation that the use of drugs in man posed special problems which were not necessarily solved by animal models. An important catalyst was the thalidomide disaster which highlighted the casual and often uninformed way in which drugs were introduced and used.

Clinical pharmacology is not merely a link between pharmacology and clinical medicine. It is a rapidly developing and evolving subject with its own methods and techniques. Although animal pharmacology provides much of the essential background to the development and use of drugs, it gives only part of the story. This is because the handling and toxicity of drugs often show considerable species difference, and also because many disease states appear to be unique to man and can therefore only be studied in the human context. In this book we portray clinical pharmacology as a subject in its own right, not as an appendage to either pharmacology or medicine. We have tried to indicate how an understanding of the subject is essential for the rational use of drugs as therapeutic agents. In a world where drugs are so widely prescribed and where many of them have so great a potential to do harm or good, the training of a doctor should include a thorough grounding in clinical pharmacology.

The importance attached to clinical pharmacology and therapeutics in the education of doctors is emphasised by the fact that in most universities in the United Kingdom it is accorded equal status with medicine, surgery and gynaecology and obstetrics in the final qualifying examination. Our objectives in this book are therefore to encourage an understanding of how drugs act and may best be used in the clinic. It is also hoped that readers will be encouraged to evaluate critically both their own clinical decisions and therapeutic innovations. In some areas we have not hesitated to introduce both complexity and controversy since clinical pharmacology is presently a rapidly changing subject. Although some of the pharmacokinetic equations are, at first sight, fearsome to many doctors of our generation it is unlikely that they will intimidate many of our students who nowadays enter our medical schools with sufficient grasp of mathematics to comprehend them with ease.

The first part of the book deals with general aspects of the subject. This section not only considers pharmacokinetics and the various factors which may modify drug disposition, but also reviews the problems of toxicity,

monitoring of adverse effects and the introduction of new drugs: topics which are important, not only to the practising doctor, but also to those concerned with drugs in industry and in government.

The second part is devoted to a systematic review of the disposition and action of drugs together with their therapeutic use. Particular emphasis is laid on side effects and interactions and where it is relevant the underlying disease processes are described.

A number of appendices which may be useful to the reader have been included. As this is not a comprehensive reference book but essentially a book for study and learning it is not fully referenced but further reading is suggested in one of the appendices. Throughout the text every effort has been made to indicate the growing points of the subject so that it is seen not as a static body of knowledge but as an expanding and developing branch of medicine.

Although this book is intended primarily for medical students, we hope that it will prove useful to those undergoing higher medical training, students of pharmacology and pharmacy and to anyone who wants to know something of this subject which has become an essential part of medical practice.

We wish to thank Dr Helen Kinsella, who helped with the correction of the text. We are extremely grateful to Mrs Christine Wier for her patient, rapid and efficient help in preparing the various drafts of the book. We also thank our many colleagues, in particular Dr Ian White and Dr Glyn Volans, who have given us help and advice. Mr Alan Whittle, our understanding publisher's reader and Miss Susan Devlin gave us invaluable assistance in preparing the book for the press.

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A. General Principles

Chapter 1
INTRODUCTION TO PHARMACOKINETICS

Pharmacokinetics may be defined as the study of the time course of absorption, distribution, metabolism and excretion of drugs and the corresponding pharmacological response. The use of mathematical models to describe these processes allows predictions to be made about such matters as drug concentration in various parts of the body, design of dosage regimes and adjustment of dosage in diseases affecting absorption, metabolism or elimination. In view of the complexity of the human body it is not surprising that pharmacokinetic formulations may be complex and require mathematical methods which can make pharmacokinetic literature and concepts unintelligible to many clinicians. In this chapter a brief synopsis of the field is given, sufficient to allow comprehension of the increasing number of publications appearing in clinical journals which make use of pharmacokinetic methods.

SINGLE-COMPARTMENT MODELS AND FIRST ORDER KINETICS

A common approach to the study of pharmacokinetic behaviour is to consider the body as a series of well-stirred compartments. These compartments have no physiological or anatomical meaning but are mathematical concepts from which a model may be built. The simplest model (Fig. 1.1) considers the body as a single compartment (a 'black box') into which the administered drug simultaneously distributes and equilibrates. This model often adequately describes the changes with time of plasma concentration or urinary excretion for drugs which rapidly distribute between plasma and tissue after administration. To assume a one-compartment model does not necessarily imply that plasma and tissue concentrations are the same, i.e. uniformity within the

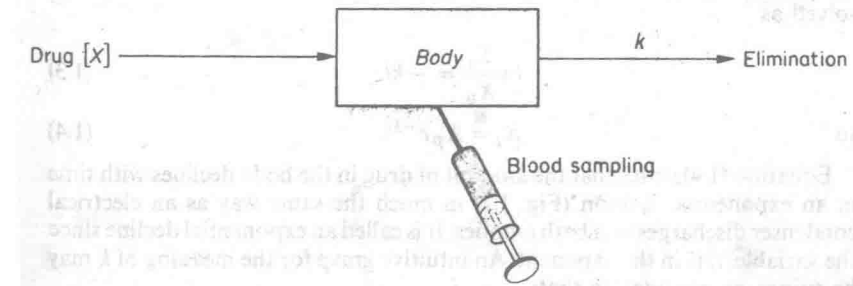

Fig. 1.1 A one-compartment model.

compartment is not necessary, but it is essential that changes occurring in the plasma quantitatively reflect changes in tissue drug levels, i.e. a constant relationship exists between these variables. Thus, if the concentration of a drug in fat at time t after a dose X is one third of the plasma concentration, then at time t after a dose $2X$ the fat concentration is still one third of the plasma concentration.

Elimination from the compartment is assumed to follow so-called first-order kinetics, i.e. the rate of a given process is proportional to the amount of drug present. To describe this it is convenient to use the methods of differential and integral calculus. Thus, the rate of change (dX/dt) in the amount of drug present in the body (X) is expressed in this notation by

$$-\frac{dX}{dt} \propto X \quad \text{so} \quad \frac{dX}{dt} = -kX, \tag{1.1}$$

where k is a proportionality constant otherwise known as the first-order elimination rate constant (its units are of time^{-1}). The negative sign in eq. (1.1) indicates drug is being lost from the body. Differential equations of this type are known as linear (the dependent variable X appears only in its first power) and homogeneous (X appears only once in every term). First-order processes therefore give rise to so-called linear kinetics. An important consequence of a linear system in kinetics is that the total area under the plasma concentration–time curve (AUC) following intravenous administration is a linear function of the administered dose. Thus doubling the dose will, other factors being equal, double the AUC. By analogy, building bricks could be considered to form a linear system in the sense that two bricks placed one on top of the other stand twice as high as a single brick. Equation (1.1) may be solved to give an expression which will allow us to obtain actual values of X at any time t by integration between the limits of zero time and t. Thus

$$\int_{X_0}^{X_t} \frac{dX}{X} = -\int_0^t k\,dt \tag{1.2}$$

which gives $\ln X_t - \ln X_0 = -kt$, where ln is the notation for logarithms (natural logarithms) taken to the base e, i.e. $\log_e$ (where e is defined as

$$e = \lim_{n \to \infty} \left(1 + \frac{1}{n}\right)^n = 2.71828\ldots)$$

and X_0 and X_t are the amounts of drug present at time 0 and time t. This is solved as

$$\ln \frac{X_t}{X_0} = -kt \tag{1.3}$$

so

$$X_t = X_0 e^{-kt}. \tag{1.4}$$

Equation (1.4) states that the amount of drug in the body declines with time in an exponential fashion (Fig. 1.2) in much the same way as an electrical condenser discharges or a bath empties. It is called an exponential decline since the variable, t, is in the exponent. An intuitive grasp for the meaning of k may be gained by considering that:

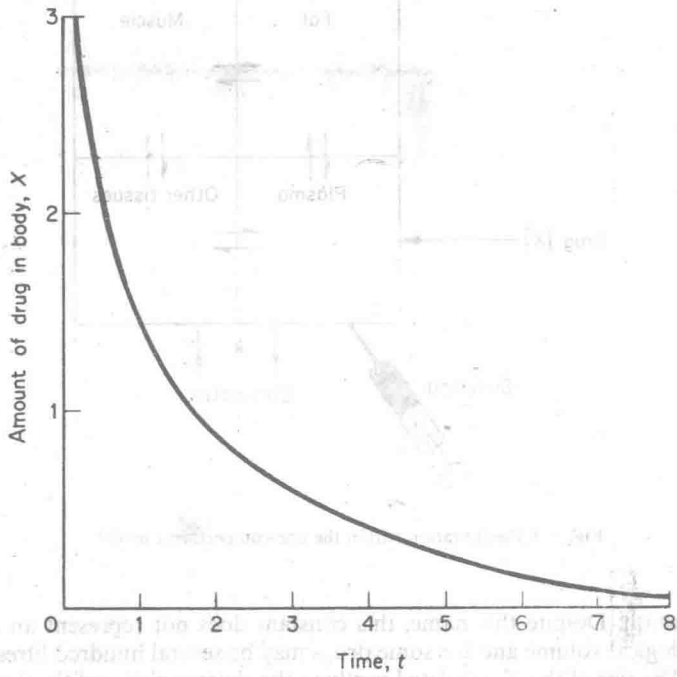

Fig. 1.2 Decline in amount of drug in body with time according to $X_t = X_0 e^{-kt}$ plotted on linear (Cartesian) coordinates.

Amount of drug eliminated in time t is

$$X_0 - X_t = X_0 - X_0 e^{-kt} = X_0(1 - e^{-kt}) \tag{1.5}$$

If a table of k in arbitrary units is prepared we have

k ($time^{-1}$)	0.001	0.01	0.1	0.2	0.3
Fraction of drug lost in unit time $(1 - e^{-k})$	0.000 999	0.009 95	0.095 2	0.181	0.259

Thus k and $(1 - e^{-k})$ are approximately equal for values of k below 0.2 and it is roughly true to say that if $k = 0.01$ hours^{-1} then 1 % of the drug in the body is eliminated per hour.

Even if the data will fit a one-compartment model obviously the drug levels in liver, heart, fat, etc, are not equal to that in plasma. The one-compartment model assumes, however, that a constant relationship exists between the drug concentration in the plasma and the amount of drug in the body (see Fig. 1.3), that is

$$X = V_d C, \tag{1.6}$$

where C is the plasma concentration and V_d is a proportionality constant which has the units of volume and is, rather confusingly, called the volume of

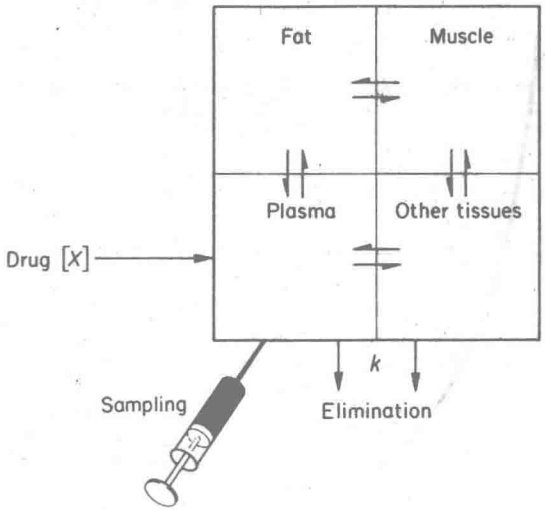

Fig. 1.3 Equilibration within the one-compartment model.

distribution. Despite this name, this constant does not represent an actual physiological volume and for some drugs may be several hundred litres in an adult. The size of the V_d is related partly to the characteristics of the drug, e.g. lipid solubility, and partly to patient characteristics such as body size, plasma protein concentration, degree of protein and tissue binding of the drug, body water and fat content. In general, drugs which are highly protein bound exhibit small V_d values, whilst highly lipid soluble compounds able to penetrate into cells and fatty tissues possess a large V_d. The V_d should be regarded as a multiplying factor relating the amount of drug in the whole body to the plasma concentration.

Example: for gentamicin the V_d is 0.25 l/kg; thus to calculate a dose of gentamicin for an 80 kg man in whom the maximum serum concentration is not to exceed 8 μg/ml, we substitute in (1.6) and

$$X = 0.25 \times 80 \times 8 = 160 \text{ mg}.$$

Use of eq. (1.6) allows eqs. (1.1)–(1.4) to be rewritten in terms of concentration. For example,

$$C_t = C_0 e^{-kt}. \tag{1.7}$$

Equation (1.7) may be rewritten as

$$\ln C = \ln C_0 - kt \tag{1.8}$$

and converted to common logarithms (i.e. logarithms to the base 10) by dividing by 2.303:

$$\log C = \log C_0 - \frac{kt}{2.303}. \tag{1.9}$$

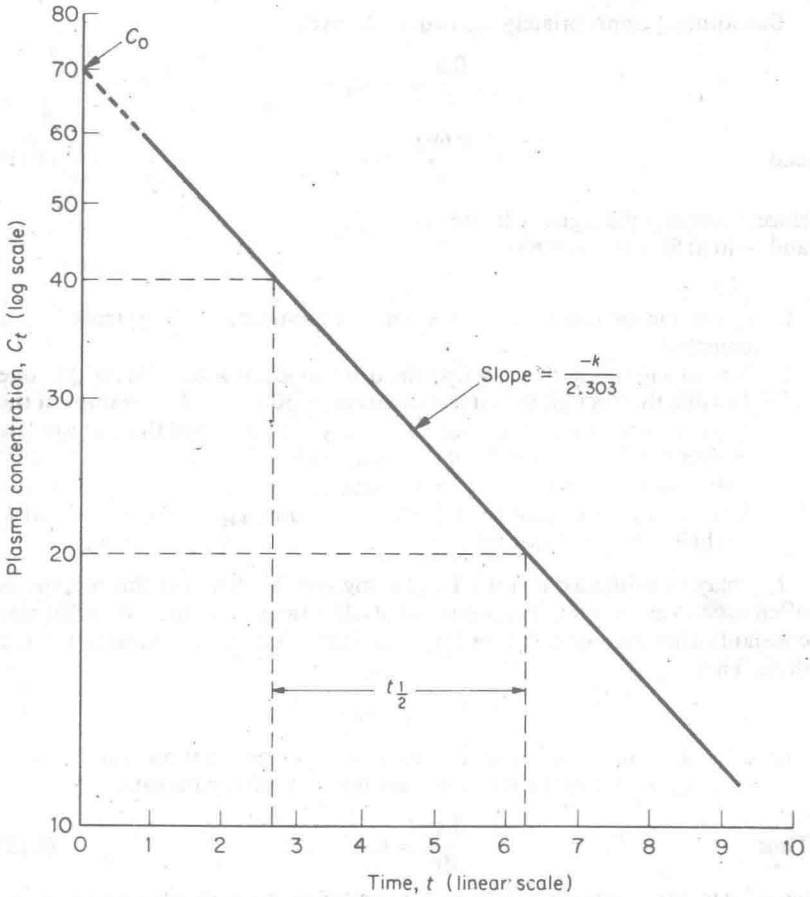

Fig. 1.4 Hypothetical plot of plasma concentration decline with time on log-linear coordinates.

Thus plotting log C against t yields a straight line and C_0 may be obtained by extrapolation of the line to zero time (Fig. 1.4). The slope of the line is $-k/2.303$. Straight lines are mathematically much easier to handle than exponential curves and so log concentration–time plots frequently occur in pharmacokinetics. Since X_0 is the dose of drug administered, eq. (1.10) may be used to find V_d from

$$V_d = \frac{X_0}{C_0}. \tag{1.10}$$

Half life and clearance

A commonly used constant to characterise first-order processes is the half-life, i.e. the time taken for the drug concentration to decline by 50%.

Substituting appropriately into eq. (1.3) gives

$$\ln \frac{0.5}{1} = -kt_{1/2},$$

and

$$\frac{0.693}{k} = t_{1/2}, \tag{1.11}$$

since, reversing the signs $-\ln(0.5) = kt_{1/2}$
and $-\ln(0.5) = \ln 2 = 0.693$.

Note that:

1. $t_{1/2}$ is independent of X_0: for linear pharmacokinetic systems it is a constant
2. It is wrong to say that because the drug concentration falls 50% in one half-life then in unit time it is decreasing by $50/t_{1/2}$%. For example if the $t_{1/2}$ is 5 hours it is correct that during any 5-hour period the *average* rate of decrease is $50/5 = 10\%$ *of the value at the start of that period* but it is untrue that 10% has gone after the first hour because k is the proportion lost per unit time and the equation preceding eq. (1.11) shows that $k = (\ln 0.5)/t_{1/2}$ and not $0.5/t_{1/2}$.

$t_{1/2}$ may be estimated directly by plotting out the data and this method is often used to ascertain k. The value of k itself is the sum of the individual rate constants characterising the various parallel elimination processes for the drug. Thus

$$k = k_r + k_{nr}, \tag{1.12}$$

where k_r = first-order rate constant for renal elimination and
k_{nr} = first order rate constant for non-renal pathways.

Thus

$$\frac{dX_u}{dt} = k_r X, \tag{1.13}$$

where dX_u/dt = urinary excretion rate of intact drug. Similar equations to those for the decline in plasma drug concentrations may be written for urinary excretion and a log/linear plot of urinary excretion rate of unchanged drug versus time may be used to determine k_r (cf. Fig. 1.4).

The $t_{1/2}$ is often regarded as a direct measure of the efficiency of drug elimination. This is incorrect since $t_{1/2}$ is dependent upon two independent variables, the volume of distribution and the total clearance of the drug (Cl):

$$t_{1/2} = \frac{0.693 V_d}{Cl}. \tag{1.14}$$

Clearance is a more accurate measure of the efficiency with which the eliminating organs remove a drug since it is defined as the fraction of the apparent volume of distribution cleared of drug by the body in unit time. Clearance is a physiologically meaningful parameter having units of flow. It is independent of the model used. Total body clearance is assessed by dividing an

intravenous bolus dose by the AUC:

$$Cl = \frac{X_0}{\int_0^\infty C\,dt} = \frac{X_0}{\text{AUC}} \tag{1.15}$$

$$= k\,V_d. \tag{1.16}$$

The area under the plasma concentration–time curve (AUC) is symbolically expressed as

$$\text{AUC} = \int_0^t C\,dt \qquad \text{for an area up to time } t$$

or $$\text{AUC} = \int_0^\infty C\,dt \qquad \text{for an area extrapolated to infinite time.}$$

Practically this may be assessed by measuring the area with a planimeter or cutting out the curve and weighing it with reference to a standard area cut from the same piece of graph paper, or most usually by a numerical approximation such as the trapezoidal rule. If the curve is fitted to a particular pharmacokinetic model, then the exact solution of the integral for that model may be used after substituting the appropriate variables derived from the data. Thus for the one-compartment model the exact solution to the integral is

$$\int_0^\infty C\,dt = \int_0^\infty C_0 e^{-kt}\,dt = \frac{C_0}{k}. \tag{1.17}$$

Thus the total body clearance for a one-compartment model is also given by substituting (1.17) into (1.15):

$$Cl = \frac{X_0 k}{C_0}. \tag{1.18}$$

In passing we may note that therefore

$$C_0 = k \int_0^\infty C\,dt \tag{1.19}$$

and this may be substituted into (1.10) to give a method for calculating the apparent volume of distribution which, because it utilises the area, is model independent:

$$V_d = \frac{X_0}{k \int_0^\infty C\,dt}. \tag{1.20}$$

Clearances are additive and total body clearance is the sum of clearance by each eliminating organ: for example,

total body clearance = renal clearance + metabolic clearance.

The maximum body clearance is determined by the blood flow through these organs and is approximately 3 l/min.

Renal clearance Cl_r is defined as the urinary drug excretion rate divided by the plasma concentration

$$Cl_r = \frac{dX_u/dt}{C}. \tag{1.21}$$

substituting from (1.13) gives

$$Cl_r = \frac{k_r X}{C}. \tag{1.22}$$

Since $X/C = V_d$ from (1.10), eq. (1.22) may also be written

$$Cl_r = k_r V_d \tag{1.23}$$

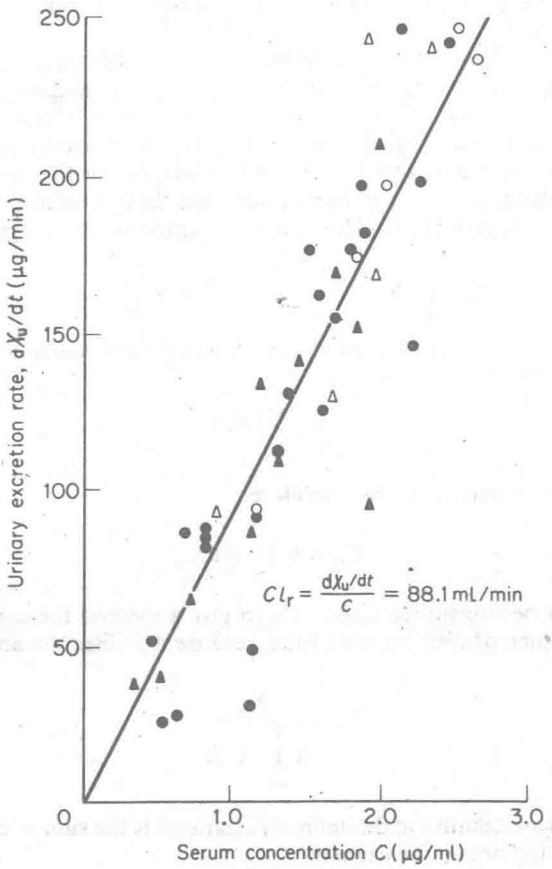

Fig. 1.5 Use of eqs (1.21) and (1.24) to determine renal clearance of tetracycline: (a) plot of mean urinary excretion rates versus serum tetracycline concentration. (b) *See facing page.*

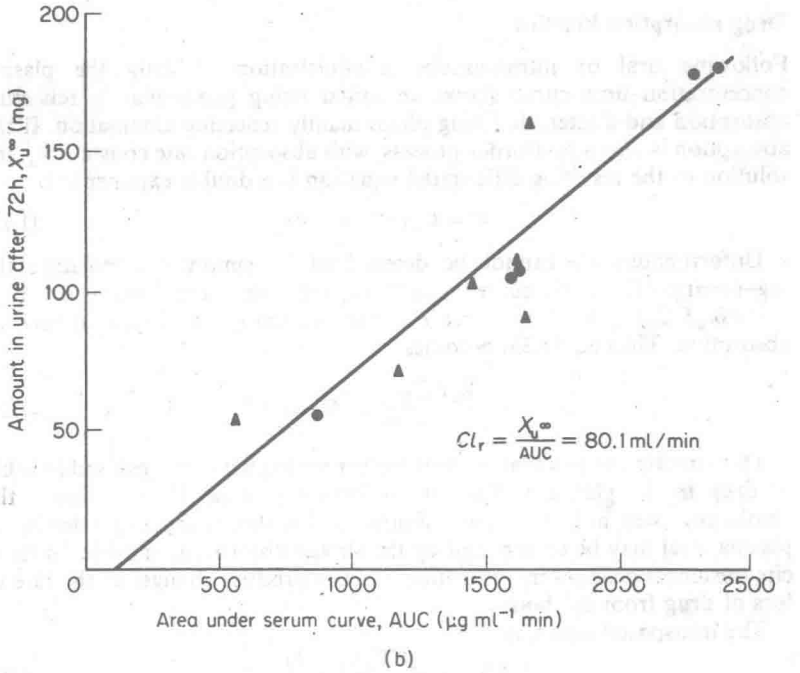

Fig. 1.5 (b) plot of cumulative tetracycline excretion in urine at 72 hours versus AUC following oral administration of 250 mg tetracycline hydrochloride. In each case the slope of the line represents renal clearance. (From W. H. Barr *et al, Clin. Pharmacol. Ther.*, **13**, 97 (1972)).

Substitution from (1.23) for Cl_r into (1.21) followed by integration from time zero to infinity and rearrangement of the equation yields an expression for average renal clearance:

$$Cl_r = k_r V_d = \frac{X_u^\infty}{\int_0^\infty C\,dt} \tag{1.24}$$

where X_u^∞ = total amount of free drug excreted in the urine (see Fig. 1.5).

Complementary changes in half-life and volume of distribution can be consistent with the same clearance. Thus a correlation has been demonstrated between half-life and age for diazepam but the clearance remains constant at all ages because of a compensatory increase in volume of distribution.

It should be noted that pharmacokinetic 'constants' are not constants in the mathematical sense. They are fitted model parameters and subject to errors in their estimation which may vary with the concentrations obtained, analytical techniques and methods of data handling. These constants result from the operation of various physiological processes and although the model used may be reasonably accurate, the model can at best only reflect the physiological situation and it should never be claimed that the true model has been found.