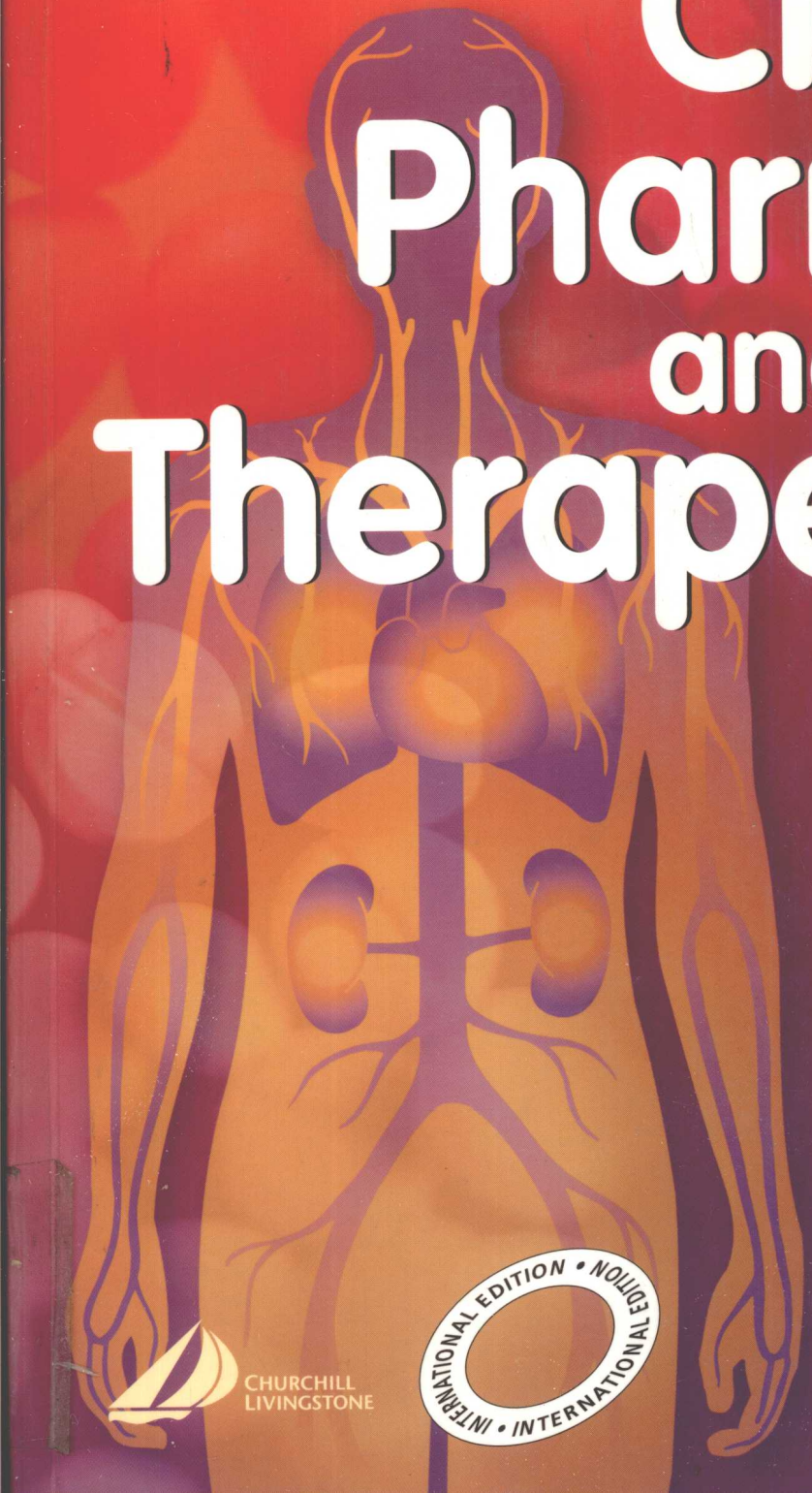
THIRD EDITION

Clinical Pharmacy and Therapeutics



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CLIVE EDWARDS

CHURCHILL LIVINGSTONE

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Clinical Pharmacy and Therapeutics

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CHURCHILL LIVINGSTONE

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Note
Medical knowledge is constantly changing. Standard safety precautions must be followed, but as new research and clinical experience broaden our knowledge, changes in treatment and drug therapy may become necessary or appropriate. Readers are advised to check the most current product information provided by the manufacturer of each drug to be administered to verify the recommended dose, the method and duration of administration, and contraindications. It is the responsibility of the practitioner, relying on experience and knowledge of the patient, to determine dosages and the best treatment for each individual patient. Neither the Publisher nor the editors/contributor assumes any liability for any injury and/or damage to persons or property arising from this publication.

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Preface

Whether in primary care or secondary care, the use of medicine is the most common intervention in health care. National strategies have emerged to promote safe, appropriate and cost effective prescribing that maximizes benefit, minimizes harm and respects patient choice. Prescribing is increasingly complex and demanding and undertaken as part of a multidisciplinary process that includes pharmacists, doctors and nurses. It is our intention that this textbook will be of value to individuals from these groups as they embark on that part of their career which specifically focuses on medicine use.

We have made every effort to update each chapter and make the content ever more relevant to practice. For the first time we have included key references in the body of the text to assist those who wish to explore the underlying evidence. In addition, and in recognition of our growing international readership, we have appointed a panel of reviewers from overseas to ensure the wider relevance of the content.

Throughout the text when using drug names we have opted to use the format Recommended International Non-proprietary Name (British approved name). With the exception of adrenaline, noradrenaline and aspirin, there will be a move to solely using rINNs and the dual naming approach of rINN (BAN) will be dropped. Given that it may be some years before full implementation, we have decided to retain the dual naming approach for this edition. We hope this helps and does not confuse.

Progress of knowledge in therapeutics is rapid, changes to dose regimens and licensed indications frequent, new medicines appear at regular intervals and guidelines for treatment of specific disorders are continually revised. Yesterday another landmark study was published. It is therefore inevitable that some sections of the book will date more quickly than others. The reader must use this text, as any other, cautiously and critically. It will then serve as a valuable learning resource, help the reader understand therapeutics and, hopefully, play a small part in achieving positive patient outcomes.

Roger Walker
Clive Edwards

Acknowledgements

We remain indebted to all the authors who have contributed to the third edition of this textbook. Their hard work, patience, tolerance and ability to meet punishing deadlines never cease to amaze. The help of many secretaries and colleagues is also acknowledged along with the wise comments from our team of international advisers. The finished product is a testament to the staff at Churchill Livingstone, who patiently edit and correct our many oversights professionally.

On a personal note we thank our close colleagues who have supported and tolerated our indulgence in editing this text. Our undergraduate and postgraduate students in clinical pharmacy at universities in Newcastle, Sunderland and Cardiff were the inspiration to produce the first edition. The feedback we continue to receive from students and practitioners, at home and abroad, sustains our commitment.

Finally, without the forbearance and understanding of our wives, Ann and Joy, there would be no book. It has been part of our lives for more than twelve years. Many domestic, social and family events have taken second place during the course of producing three editions. We are eternally grateful for their continued support.

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Contents

SECTION 1

GENERAL

1 Practical pharmacokinetics

R. Fitzpatrick

KEY POINTS

- Pharmacokinetics can be applied to a range of clinical situations with or without therapeutic drug monitoring (TDM).
- TDM can improve patient outcomes but is only necessary for drugs with a low therapeutic index, where there is a good concentration response relationship, and where there is no easily measurable physiological parameter.
- Sampling before steady state is reached or before distribution is complete leads to erroneous results.
- The volume of distribution can be used to determine the loading dose.
- The elimination half-life determines the time to steady state and the dosing interval.
- Kinetic constants determine the rate of absorption and elimination.
- Clearance determines the maintenance dose.
- Creatinine clearance can be reliably estimated from population values.
- Wherever possible use actual blood level data to assist dose adjustment. However, population pharmacokinetic values can be used for digoxin, theophylline, and gentamicin.
- Once daily dosing of gentamicin is a realistic alternative to multiple dosing.
- TDM is essential in the dose titration of lithium and phenytoin, but of little value for valproate, or the newer anticonvulsants.

Clinical pharmacokinetics may be defined as the study of the time course of the absorption, distribution, metabolism and excretion of drugs and their corresponding pharmacological response. In practice, pharmacokinetics makes it possible to model what may happen to a drug after it has been administered to a patient. Clearly, this science may be applied to a wide range of clinical situations, hence the term 'clinical pharmacokinetics'.

General applications

Clinical pharmacokinetics can be applied in daily practice for drugs with a low therapeutic index, even if drug level monitoring is not required.

Time to maximal response

By knowing the half-life of a drug, the time to reach a steady state may be estimated (Fig. 1.1), and thus when maximal therapeutic response is likely to occur, irrespective of whether drug level monitoring is needed.

Need for a loading dose

The same type of information can be used to determine whether a loading dose of a drug is necessary, since drugs with longer half-lives are more likely to require loading doses for acute treatment.

Dosage alterations

Clinical pharmacokinetics can be useful in determining dosage alteration if the route of elimination is impaired through end organ failure (e.g. renal failure) or drug interaction. Using limited pharmacokinetic information such as the fraction excreted unchanged (f_e value), which can be found in most pharmacology textbooks, quantitative dosage changes can be estimated.

Choosing a formulation

An understanding of the pharmacokinetics of absorption may also be useful in evaluating the appropriateness of particular formulations of a drug in a patient.

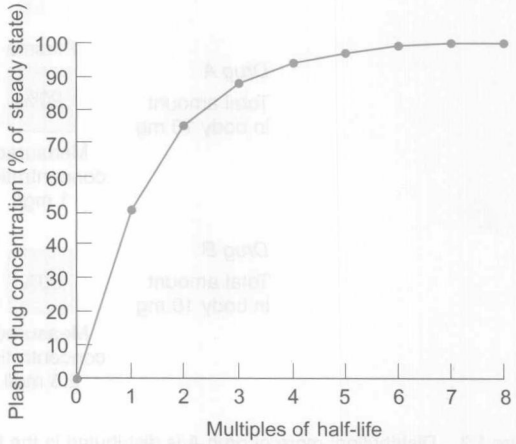

Figure 1.1 Time to steady state.

Application to therapeutic drug monitoring (TDM)

Clinical pharmacokinetics is usually associated with therapeutic drug monitoring (TDM), and its subsequent utilization. When TDM is used appropriately, it has been demonstrated that patients suffer fewer side-effects than those who were not monitored (Reid et al 1990). Although TDM is a proxy outcome measure, a study with aminoglycosides (Crist et al 1987) demonstrated shorter hospital stays for patients where TDM was used. Furthermore, a study on the use of anticonvulsants (McFadyen et al 1990) showed better epilepsy control in those patients where TDM was used.

There are various levels of sophistication for the application of pharmacokinetics to TDM. Knowledge of the distribution time and an understanding of the concept of steady state can facilitate determination of appropriate sampling times.

For most drugs that undergo first-order elimination, a linear relationship exists between dose and concentration, which can be used for dose adjustment purposes. However, if the clearance of the drug changes as the concentration changes (e.g. phenytoin), then an understanding of the drug's pharmacokinetics will assist in correct dose adjustments.

More sophisticated application of pharmacokinetics involves the use of population pharmacokinetic data to produce initial dosage guidelines, for example nomograms for digoxin and gentamicin, and to predict drug levels. Pharmacokinetics can also assist in complex dosage individualization using actual patient-specific drug level data.

Given the wide range of clinical situations in which pharmacokinetics can be applied, pharmacists must have a good understanding of the subject and how to apply it in order to maximize their contribution to patient care.

Basic concepts

Volume of distribution

The apparent volume of distribution (V_d) may be defined as the size of a compartment which will account for the total amount of drug in the body (A) if it were present in the same concentration as in plasma. This means that it is the apparent volume of fluid in the body which results in the measured concentration of drug in plasma (C) for a known amount of drug given, i.e.

$$C = \frac{A}{V_d}$$

This relationship assumes that the drug is evenly distributed throughout the body in the same concentration as in the plasma. However, this is not the case in practice, since many drugs are present in different concentrations in various parts of the body. Thus, some drugs such as digoxin have a very large apparent volume of distribution. This concept is better explained in Figure 1.2.

Apparent volume of distribution may be used to determine the plasma concentration after an intravenous loading dose:

$$C = \frac{\text{loading dose}}{V_d} \quad (1)$$

Conversely, if the desired concentration is known, the loading dose may be determined:

$$\text{loading dose} = \text{desired } C \times V_d \quad (2)$$

In the previous discussion, it has been assumed that after a given dose a drug is instantaneously distributed between the various tissues and plasma. In practice this

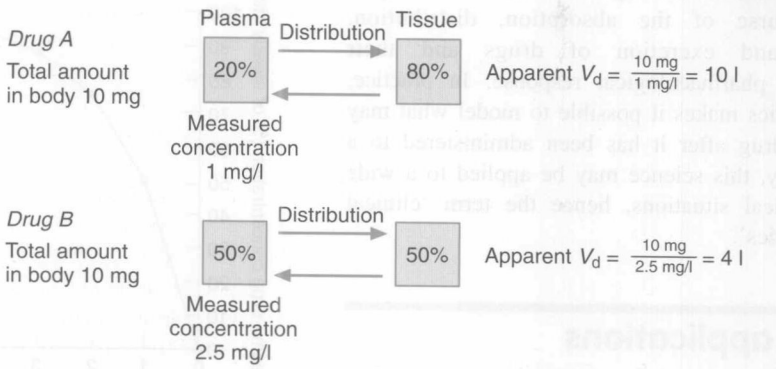

Figure 1.2 Distribution: more of drug A is distributed in the tissue compartment resulting in a higher apparent volume of distribution than drug B, where more remains in the plasma.

is seldom the case. Although a drug may be distributed into many tissues, it is reasonable for practical purposes to generalize by referring to tissue as if it were a single entity or compartment. Thus, the body may be described in pharmacokinetic terms as if it were divided into two compartments: the plasma and the tissues.

Figure 1.3 depicts the disposition of a drug immediately after administration and relates this to the plasma concentration–time graph.

Initially, the plasma concentration falls rapidly, due to distribution and elimination (α phase). However, when an equilibrium is reached between the plasma and tissue (i.e. distribution is complete) the change in plasma concentration is due to elimination from the plasma (β phase), and the plasma concentration falls at a slower rate. The drug is said to follow a two-compartment model.

However, if distribution is completed quickly (within minutes), then the α phase is not seen, and the drug is said to follow a one-compartment model.

The practical implications of a two-compartment model are that any sampling for serum concentration monitoring purposes should be carried out after distribution is complete, and intravenous bolus doses should be given slowly to avoid transient side-effects due to high peak concentrations.

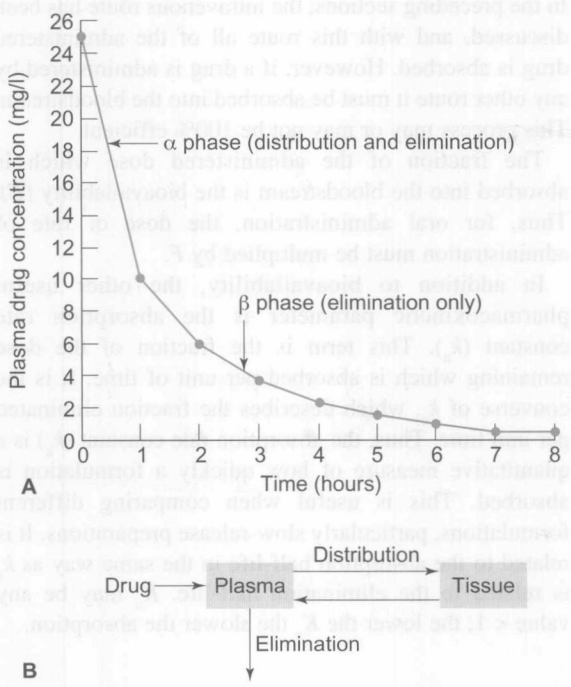

Figure 1.3 **A** Two-compartment model showing two phases in the plasma concentration-time profile. **B** representation of a two-compartment model showing distribution of drug between plasma and tissue compartments.

Elimination

Drugs may be eliminated from the body by a number of routes. The primary routes are metabolism (usually in the liver) into an inactive compound, excretion of the unchanged drug in the kidneys, or a combination of both.

The main pharmacokinetic parameter describing elimination is clearance *(CL)*. This is defined as the volume of plasma completely emptied of drug per unit time. For example, if the concentration of a drug in a patient is 1 g/l and the clearance is 1 l/h, then the rate of elimination will be 1 g/h.

Thus, a relationship exists:

$$\text{rate of elimination} = CL \times C \qquad (3)$$

Total body elimination is the sum of the metabolic rate of elimination and the renal rate of elimination. Therefore:

$$\text{total body clearance} = CL\ (\text{metabolic}) + CL\ (\text{renal})$$

Thus, if the fraction eliminated by the renal route is known (f_e), then the effect of renal impairment on total body clearance can be estimated.

For most drugs, clearance is constant. Therefore, it is clear from equation (3) that as the plasma concentration changes so will the rate of elimination. However, when the rate of administration is equal to the rate of elimination, the plasma concentration is constant (C^{ss}) and the drug is said to be at a steady state. At steady state:

$$\text{rate in} = \text{rate out}$$

At the beginning of a dosage regimen the plasma concentration is low. Therefore, the rate of elimination is less than the rate of administration, and accumulation occurs until a steady state is reached (see Fig. 1.1).

$$\text{rate of administration} = \text{rate of elimination} = CL \times C^{ss} \qquad (4)$$

It is clear from equation (3) that as the plasma concentration falls (e.g. on stopping treatment or after a single dose), the rate of elimination also falls. Therefore, the plasma concentration–time graph follows a non-linear curve characteristic of this type of first-order elimination (Fig. 1.4). This is profoundly different from a constant rate of elimination irrespective of plasma concentration, which is typical of zero-order elimination.

For drugs undergoing first-order elimination, there are two other useful pharmacokinetic parameters in addition to the volume of distribution and clearance. These are the elimination rate constant and elimination half-life.

The elimination rate constant (k_e) is the fraction of the amount of drug in the body eliminated per unit time. For example, if the body contains 100 mg of a drug and 10% is eliminated per unit time, then $k_e = 0.1$. In the first unit of time, 0.1 × 100 mg or 10 mg is eliminated, leaving 90 mg. In the second unit of time, 0.1 × 90 mg or 9 mg is