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FOREWORD BY O H WOLFF

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edited by

H. B. Valman, MD FRCP DCH
Consultant Paediatrician
Northwick Park Hospital and
Clinical Research Centre,
Harrow, Middlesex

foreword by

Professor O. H. Wolff
Nuffield Professor of Child Health
Institute of Child Health
London

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Contributors

C. J. BACON MB MRCP First assistant, Department of Child Health, University of Newcastle upon Tyne.

T. M. BARRATT FRCP Consultant Paediatrician, Hospital for Sick Children, Great Ormond Street, London; Senior Lecturer in Paediatric Nephrology, Institute of Child Health, London.

B. D. BOWER MD FRCP Consultant Paediatrician, The Radcliffe Infirmary, Oxford.

PAMELA A. DAVIES MD FRCP DCH Reader in Paediatrics, Institute of Child Health, London; Honorary Consultant Paediatrician, Hammersmith Hospital, London.

D. B. GRANT MD FRCP Consultant Paediatrician, Hospital for Sick Children, Great Ormond Street, London.

R. S. JONES MD FRCP DCH Consultant Clinical Physiologist, Royal Liverpool and Alder Hey Children's Hospitals; Director of Studies in Paediatric Science, and Clinical Teacher, Department of Child Health, University of Liverpool.

T. J. McELWAIN MB FRCP Consultant Physician, Royal Marsden Hospital, Sutton, Surrey.

J. C. MUCKLOW MD MRCP Lecturer in Clinical Pharmacology, University of Newcastle upon Tyne.

M. D. RAWLINS BSC MD FRCP Professor of Clinical Pharmacology, University of Newcastle upon Tyne.

P. A. ROUTLEDGE MB MRCP Senior Research Associate, Department of Pharmacological Sciences (Clinical Pharmacology), University of Newcastle upon Tyne.

H. SIMPSON MD FRCP DCH Consultant Paediatrician, Royal Hospital for Sick Children, Edinburgh.

JEAN M. SMELLIE BM FRCP DCH Consultant Paediatrician, University College Hospital and Medical School, London.

H. B. VALMAN MD FRCP DCH Consultant Paediatrician, Northwick Park Hospital and Clinical Research Centre, Harrow, Middlesex.

Foreword

The last few decades have seen great progress in our understanding of the scientific basis of paediatrics. The application of the science of clinical pharmacology to paediatrics is of more recent origin. For too long it has been assumed that the results of studies of drug metabolism in the adult are also applicable during the period of human development from conception onwards. The fallacy and the dangers of such assumptions are becoming clearer as many new drugs with powerful therapeutic and equally powerful toxic potential are becoming available for the treatment of disease in children and pregnant women. There is need for much research into the effects of drugs on the developing human being and for a critical appraisal of the ethical problems involved in such research.

The first three chapters of this book provide the clinician with the basic knowledge necessary for the intelligent use of drugs in childhood. The subsequent chapters deal with the management of some common paediatric conditions, and also other less common ones where there have been important advances in therapy. Each chapter is written by an expert in the field, who has personally contributed to improvement in treatment.

The editor, Dr Valman, has been wise in his choice of conditions included in this volume and of contributors, all of whom succeed not only in presenting clearly the important advances, but also in giving their personal approach to management. A writer of a chapter on treatment faces a dilemma: is he to include matters of aetiology and diagnosis which have a bearing on therapy, or is he to confine his remarks to therapy? If he chooses the first alternative, the book will become yet another textbook of paediatrics. If he chooses the second, there is the danger of the volume becoming a 'cookery book' consisting of a series of recipes. The contributors, no doubt on the advice of the editor, have avoided either extreme and their chapters cover those aspects of aetiology, pathogenesis, and diagnosis without which a rational discussion of treatment is impossible.

In parallel with progress in clinical pharmacology many advances

have been made in recent years in our understanding of social and emotional factors in childhood disease. A sensitive awareness of such factors will influence the doctor's concept of, and practical approach to, treatment. The reader of this volume will be left in no doubt that modern therapy consists of more than the intelligent use of drugs.

London, September 1978 *O. H. Wolff*

Preface

What is the use of a book on treatment without methods of diagnosis? Although an accurate diagnosis is essential for optimal treatment, major changes in methods of diagnosis occur less frequently than new approaches to treatment. Improved results do not always require new drugs but may be achieved, as in leukaemia, by more effective use of old drugs or even by avoiding them. A book on therapeutics can be revised more frequently than a standard textbook and enable the reader to see recent advances.

In contrast to a chemical reaction in a laboratory, the effect of a drug on a particular patient cannot be predicted. The pharmacology of the drug, the natural history of the disease and the social and emotional effects of the disease and treatment need to be considered before giving the drug. If the treatment fails, all these factors need to be considered again to determine whether the dose of the drug should be raised or another drug added or substituted.

This book aims to bring together the scientific principles of pharmacologists and the practical experience of clinicians in the management of common paediatric therapeutic problems. The first three chapters deal with some aspects of clinical pharmacology and each of the remaining chapters is concerned with a specific clinical problem and is written by a clinician who is an authority in that field. It has been written for the medical and nursing staff of paediatric units, family doctors and undergraduates.

London, September 1978 *H. B. Valman*

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I am extremely grateful to Professor O. H. Wolff for writing the foreword. I would like to thank the authors for generously giving their time to write the chapters and to their families for accepting the deprivation that this has entailed. I thank the authors and publishers who have allowed us to reproduce their material.

I thank Mr Peter Saugman for his imaginative efforts during the conception, development and delivery of this book. Mr John Robson deserves special praise for producing this volume in record time.

Contents

CHAPTER 1

Pharmacokinetics including therapeutic use of blood levels

J. C. Mucklow, C. J. Bacon & M. D. Rawlins

Pharmacokinetics is the study of the relationships between drug concentrations in biological fluids, the magnitude of drug effects (pharmacological, therapeutic and toxic), and their time course. Although a few drugs can be directly applied to the organ or tissue where they act (e.g. local anaesthetics, topical steroids, inhaled bronchodilators) most must reach the general circulation before they gain access to their 'target organs'. It is partly for this reason, and partly due to the problems of measuring drug concentrations in tissues, that pharmacokinetics is mainly concerned with blood and plasma concentrations of drugs.

Many of the pharmacokinetic properties of a drug are governed by its facility to diffuse across the lipid bilayers of cell membranes. Drugs which are non-polar (and soluble in lipid) will readily diffuse across the gastrointestinal epithelium, will be widely distributed into various tissues and organelles, and undergo extensive renal tubular reabsorption by diffusion across the tubular epithelium. Such drugs will therefore undergo elimination by metabolism to more polar derivatives which will be excreted in the urine. By contrast, polar drugs (which are relatively insoluble in lipid but soluble in water) will be less readily absorbed from the gut, less widely distributed outside the circulation, and will undergo extensive renal excretion.

Most drugs are weak electrolytes and can exist in two states—ionised or non-ionised. Drugs which are weak acids (e.g. salicylate, penicillins, warfarin, barbiturates) become more ionised as the pH of the solution rises: drugs which are weak bases (e.g. paracetamol, propranolol, benzodiazepines) will become more ionised as the pH

of the solution falls. The ionised moiety is not lipid soluble and only non-ionised molecules can diffuse across cell membranes (Fig. 1.1).

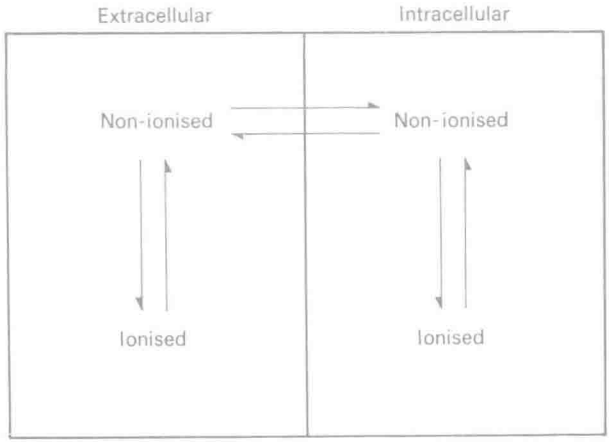


Fig. 1.1 Equilibrium between extracellular and intracellular drug molecules.

ZERO- AND FIRST-ORDER PROCESSES

The rates at which drugs enter and leave the body may be either zero-order or first-order processes.

First-order kinetics

Most drugs are absorbed and eliminated by first-order reactions. Thus, a constant fraction (or proportion) of the drug is absorbed or eliminated per unit time. In these circumstances, the rate of drug movement (e.g. in mg/hour) is not constant, but is proportional to the amount of drug which has to be moved:

$$\frac{dX}{dt} \propto X \qquad \textit{equation 1}$$

when X is the amount of drug, t is time, and dX/dt is the rate of change (e.g. by absorption or elimination). From this equation it is obvious that when X is large, dX/dt will be large, and when X is small dX/dt will also be small. X and dX/dt can be equated thus:

$$\frac{dX}{dt} = -k \,.\, X \qquad \textit{equation 2}$$

where k is the first-order rate constant and the right-hand side of the equation rendered negative because X is decreasing. The first-order rate constant represents the fraction of X which undergoes movement per unit time and has units of reciprocal time (e.g. min^{-1}, $hours^{-1}$, $days^{-1}$). Integration of *equation 2* yields:

$$X = X_0 e^{-kt} \qquad \textit{equation 3}$$

and a graph of X against t is curvilinear (Fig. 1.2A).

Taking natural logarithms:

$$\ln X = \ln X_0 - kt \qquad \textit{equation 4}$$

where X_0 is the amount of drug at zero time. Plotting $\ln X$ against t (Fig. 1.2B) yields a straight line with slope equal to $-k$ and intercept on the ordinate of $\ln X_0$.

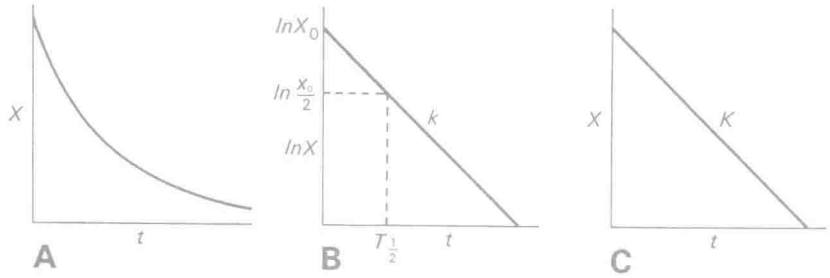


Fig. 1.2 Elimination of drug (X) per unit time (t); A, first-order; B, first-order, logarithmic plot; C, zero-order.

The time taken for the amount of drug to fall by half is its half-life ($T_{\frac{1}{2}}$). This is the time taken for X_0 to fall to $X_0/2$ and substituting in *equation 4*:

$$ln\frac{X_0}{2} = \ln X_0 - k \,.\, T_{\frac{1}{2}}$$

$$k \,.\, T_{\frac{1}{2}} = \ln X_0 - \ln\frac{X_0}{2} = \ln \frac{X_0}{0.5X_0} = \ln 2$$

then

$$k \,.\, T_{\frac{1}{2}} = \ln 2 = 0.693$$

so that k and $T_{\frac{1}{2}}$ are inversely related:

$$k = \frac{0.693}{T_{\frac{1}{2}}} \quad \text{and} \quad T_{\frac{1}{2}} = \frac{0.693}{k} \qquad \textit{equation 5}$$

Zero-order kinetics

In some instances drugs are absorbed or eliminated at a constant rate. Thus, a continuous intravenous infusion delivers drug at a fixed amount per unit time. Elimination may also be zero-order if the removal process reaches saturation (e.g. phenytoin and alcohol). In both instances the rate of change (dX/dt) is a constant (K):

$$\frac{dX}{dt} = -K$$

which on integration yields

$$X = X_0 - Kt \qquad \textit{equation 6}$$

so that a graph of X against t is linear with slope K (Fig. 1.2C).

DRUG ABSORPTION

Two pharmacokinetic parameters are concerned with drug absorption.
1 Absorption rate is usually (though by no means invariably) first-order, except in the case of intravenous infusion (zero-order) and intravenous injection (instantaneous). It is usually assessed from the absorption half-life, or absorption rate constant (see *equation 5*). After oral administration, drug absorption rates are largely determined by the polarity of the drug, the pharmaceutical formulation and, most important of all, the rate of gastric emptying. Factors which alter gastric emptying (food, intragastric pH, fear, pain, nausea, drugs) have potent effects on the rate of drug absorption.
2 Bioavailability is the fraction of a dose which reaches the systemic circulation. For drugs given parenterally, it is clearly unity. For drugs given enterally, however, bioavailability may be less than one, either if there is incomplete absorption from the gastrointestinal tract (e.g. digoxin, guanethidine) or because of metabolism of the drug during its passage across the gut wall or through the liver (e.g. propranolol, lignocaine). The importance of this metabolic process, which is often

referred to as 'first-pass' elimination, varies for different drugs and also varies between individuals for the same drug.

DRUG DISTRIBUTION

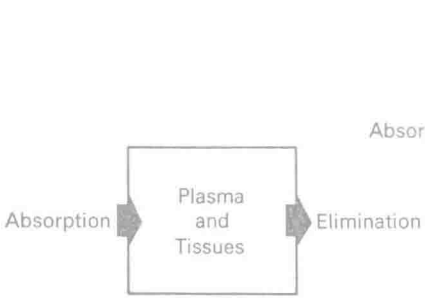
Drugs leave the systemic circulation primarily by diffusion—a process which is once again determined by lipid solubility. The extent to which drugs are distributed extravascularly can be measured by determining the distribution volume (V_d). However, this volume is an apparent space and does not represent any anatomical compartment except for certain special compounds (e.g. antipyrine, which is distributed throughout total body water). V_d is the volume occupied by a drug, assuming its extravascular concentration is the same as that in plasma:

$$V_d = \frac{\text{drug in body}}{\text{plasma concentration}} \qquad \textit{equation 7}$$

with dimension of litres (or l/kg body weight). Since many drugs are sequestered in various tissues (by solution in body fat, or by binding to tissue proteins), V_d may be appreciably larger than is possible physiologically. For example, nortriptyline has a V_d of 20–50 l/kg body weight, and one can immediately infer that this drug is extensively distributed outside the circulation. By contrast, warfarin has a V_d of 0.1–0.2 l/kg suggesting that a large proportion of the drug is confined to plasma.

The simplest model of drug distribution is the so-called 'one-compartment open model' (Fig. 1.3). Rapid equilibration of drug takes place between the plasma and extravascular tissues, so that the entire volume through which the drug is distributed can be considered as one compartment. Antipyrine (Phenazone) is a classic example of this model.

For many drugs, however, a one-compartment model is inappropriate since equilibration between plasma and tissues occurs much more slowly. The decline in plasma concentration is accordingly multiexponential and kinetic parameters such as elimination rate constant, half-life and apparent volume of distribution can be calculated only by the use of more complex two-compartment or even three-compartment models (Fig. 1.4).



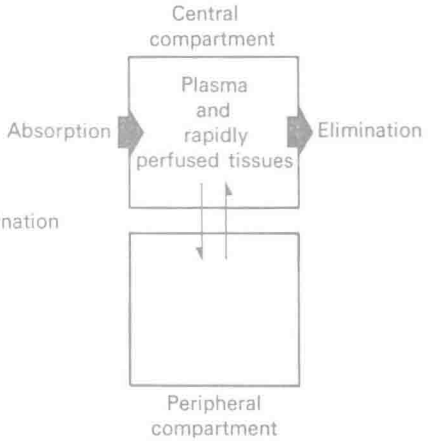


Fig. 1.3 (left). Drug distribution; one-compartment open model.
Fig. 1.4 (right). Drug distribution; two-compartment model.

DRUG ELIMINATION

The most useful pharmacokinetic parameter for assessing the rate at which a drug is eliminated is its clearance. Plasma drug clearance is analogous to renal clearance and represents the volume of plasma completely cleared of drug per unit time. It may be calculated thus:

$$\text{Clearance} = V_d \times k_{el} \qquad \textit{equation 8}$$

where k_{el} is the elimination rate constant. The total plasma clearance of a drug is the sum of its renal and metabolic clearances:

$$Cl_{total} = Cl_{renal} + Cl_{metabolic} \qquad \textit{equation 9}$$

and may vary from 2–3 ml/min (for warfarin) to 800 ml/min (for propranolol). The renal clearance (Cl_{renal}) of a drug and glomerular filtration rate are closely correlated. For drugs where $Cl_{metabolism}$ is small and Cl_{renal} approximates to Cl_{total}, an individual's glomerular filtration rate (or, more usually, creatinine clearance) provides a good indication of his drug clearance. This relationship is particularly useful in predicting digoxin and gentamicin dosages for patients with impaired renal function.

Those drugs which undergo extensive hepatic metabolism can be