Drug Disposition and Pharmacokinetics

From Principles to Applications

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Preface

The origins of this book can be traced to a previous book with the same title written by one of us (S.H.C.) in 1974, second and third editions being published in 1977 and 1980. At the time, we were both in the early stages of what has become a very enjoyable career-long collaboration. Since that time newer approaches to the subject have been developed and many other books have been published. Mostly these have tended to be either very basic texts on pharmacokinetics, or weightier tomes, although some have been brief introductory texts, while yet others have concentrated on clinical applications. We have aimed to produce a book that takes the middle road, providing sufficient information and background to make it informative, clear, readable and enjoyable, without unnecessary complexity, maintaining the philosophy of the original *Drug Disposition and Pharmacokinetics*. Consequently, this book should be of benefit, in particular, to undergraduate and postgraduate students of science, including pharmacology, toxicology, medicinal chemistry and basic medical science, and students preparing for, and in, pre-professional programmes such as those in pharmacy, medicine and related disciplines, including dentistry and veterinary science, and environmental and public health. However, we are all life-long students, and thus this book is for anyone at any stage in his or her career wishing to learn about drug disposition and pharmacokinetics, that is, what happens to drug molecules in the body, but with strong emphasis on the pharmacological and clinical consequences of drug consumption, and so we expect our book to find readers among researchers, teachers and students in universities, in research institutes, in the professions, in industry, and in public laboratories employing toxicologists and environmental scientists in particular.

Clearly pharmacokinetics cannot be taught without recourse to mathematics. However, understanding the equations in this book requires little more than a basic knowledge of algebra, laws of indices and logarithms and very simple calculus. Anyone wishing to refresh his or her knowledge in these areas is recommended to read the Appendix. In a practical sense, it is important to be able to match standard equations to common graphical displays. There is little need in this context for the ability to derive complex equations. We believe in the old maxim, that a picture is worth a thousand words, and have noted that many of the principal pharmacokinetic relationships can be demonstrated empirically by the movement of dye into and out of volumes of water. We have used this approach to illustrate the validity of several models and further examples and colour plates can be found on the companion web site. This site also contains more mathematical examples, further equations and worked examples for readers who require them.

With few exceptions, we have adopted the system of pharmacokinetic symbols recommended by Aronson and colleagues (*Eur J Clin Pharmacol* 1988; 35: 1) where C represents concentration, A, is used for quantities or amounts, V for volumes of distribution, Q for flow rates, etc. First-order rate constants are either k or, if they are *elimination* rate constants, λ. Numbers have been used to designate compartments rather than letters (letters can lead to confusion, for example between plasma and peripheral) and for the exponents in multiple-compartment models. Thus, the variables for the biphasic decline of a two-compartment model are C_1, C_2, λ_1 and λ_2 rather than A, B, α and β, which may be familiar to some readers. It has not been possible to select a single convention for drug nomenclature. Rather, the names most likely to be familiar to readers around the world are used, and so we have leaned towards

recommended International Non-proprietary Names (rINN). In most instances this should not cause problems for the majority of readers: cyclosporin, cyclosporine and ciclosporin clearly refer to the same drug. Where names are significantly different, alternatives are given in parentheses, e.g. pethidine (meperidine), and in the Index.

We have designed this book to be read from beginning to end in the order that we have presented the material. However, there is extensive cross-referral between sections and between chapters – this should aid those readers who prefer to 'dip in,' rather than start reading from Page 1. Thus, Chapter 1 is a brief presentation of the general chemical principles underlying the key mechanisms and processes described in the later chapters, effectively a mini-primer in medicinal chemistry. Drug disposition and pharmacokinetics is a discipline within the life sciences that depends entirely on these and other chemical principles. Chapters 2 and 3, which detail distribution and fate of drugs, are largely descriptive. Pharmacokinetic modelling of drug and metabolites, including more advanced concepts of clearance can be found in Chapters 4– 7. Chapter 8 is devoted to bioavailability, particularly the influence of tablet formulation on concentrations of drugs in plasma and therefore on clinical outcome. The next four chapters (9–12) deal with what can be referred to as 'special populations' or 'special considerations': sex, disease, age and genetics in particular. The relationships between pharmacokinetics and pharmacological and clinical effects (PK-PD) are the topic of Chapters 13 and 14, whilst extrapolation from animals to human beings is considered in Chapter 15. The kinetics of macromolecules, including monoclonal antibodies, are considered in Chapter 16. The final chapters exemplify the importance of pharmacokinetics in three clinical areas, considering aspects of drug interactions, toxicity and therapeutic drug monitoring. Thus our sequence is from scientific preparation, through relevant science, to an introduction to clinical applications. The logical extension of the learning process in this area would be obtainable through one or more of the excellent texts available that focus on patient-care orientated pharmacokinetic research and practice.

Our examples come from our own experience, from literature of pivotal significance in the development of the subject, and from drugs that will be especially familiar to readers. Certain drugs stand out as demonstrating basic principles of widespread significance throughout the subject. They include propranolol, warfarin, digoxin, aspirin, theophylline and isoprenaline. It should be noted that these, and several other examples, can be considered as 'old' drugs. Some, indeed, such as isoprenaline and guanethidine, are obsolete as therapeutic agents, but still of paramount importance historically and as models. It was with these and other long-established drugs that principles of lasting significance were discovered. Of relevance to this is the fact that interest in this area of science undoubtedly existed among the ancients. More recently, Shakespeare referred to the risk–benefit ratio associated with alcohol consumption in *Macbeth*, and to the duration of action of the fantasy drug consumed by Juliet in *Romeo and Juliet*. Henry Bence Jones was probably the first to describe the rates of transfer of drugs between tissues, in work conducted in the 1860s, after he had developed assays for lithium and quinine. Awareness of the first-order removal of digoxin from the body originates from Gold *et al*. in the 1920s. However, it was in the 1930s that Widmark and Teorell first examined concentrations in blood. In the 1950s and 1960s, Brodie and Williams focused our interest on metabolism and metabolites, and then on quantitative pharmacology related to concentrations in blood. The big explosion of interest resulted from stirrings of pharmacokinetic thought in the colleges of pharmacy, and from the development of Clinical Pharmacology primarily in medical schools, in the 1960s, 1970s, and 1980s. It has been exciting to be associated with this dramatic development in medical science. Mathematical pharmacokinetics first gained prominence in relation to dosage form design, then to profiling of drugs in humans and control of clinical response, and, remarkably, only recently, in the process of new drug discovery.

We have not discussed bioanalysis, apart from a brief consideration of assay specificity in Chapter 19. However, it is important that the reader be aware that pharmacokinetic information can be no better than the quality of the concentration–time data provided. Thus, the pharmacokineticist should ensure that concentration data are from specific, precise and accurate assays, including their application to error-free timing of sample collections. Notes on other methods of drug investigation are to be found throughout the book, and

readers interested in particular methods should be able to access relevant information through the index and references.

We hope that you enjoy this book. We thank our various students in London, Gainesville, Rochester, and too many other locations to mention, for their help in formulating our understanding of our readers' needs in this subject area, and dedicate this book to them. We are immensely grateful to our publishers for their sage advice, and to our families for their support, tolerance and encouragement during the writing of this book.

Stephen H. Curry, Rochester, New York,
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January 2010

About the Authors

Stephen Curry

Stephen has been Professor of Pharmacology at The London Hospital Medical College, Professor of Pharmaceutical Science at the University of Florida, and Adjunct Professor of Pharmacology and Physiology at the University of Rochester. He has also spent ten years with AstraZeneca and predecessor companies. He was honoured by the Faculty of Medicine of the University of London with the Doctor of Science Degree and is a Fellow of the Royal Pharmaceutical Society. He currently works in the field of technology transfer and translational science with early stage companies based on discoveries at the University of Rochester (PharmaNova) and Cornell University (ADispell). He can be contacted at www.stephenhcurry.com.

Robin Whelpton

After obtaining his first degree in Applied Chemistry, Robin joined the Department of Pharmacology and Therapeutics, London Hospital Medical College, University of London as research assistant to Professor Curry. Having obtained his PhD in pharmacology, he became lecturer and then senior lecturer before transferring to Queen Mary University of London, teaching pharmacology to preclinical medical students. He is currently a member of the School of Biological & Chemical Sciences and has a wealth of experience teaching drug distribution and pharmacokinetics to undergraduate and postgraduate students of medicine, pharmacology, biomedical sciences, pharmaceutical chemistry and forensic science.