'Introduction to drug disposition and pharmacokinetics' by Stephen H Curry and Robin Whelpton

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This book is well written and logically organized, including a large number of appropriately chosen color illustrations and tables. There is a logical flow from the introduction to the concluding chapter, which seamlessly allows the integration of a wide range of topics rather than treating them as isolated academic chapters. However, it is possible to choose selected topics. For example, those wishing to get a better understanding of the basic mathematical techniques in pharmacokinetics could do well to read the first Chapter, 'Introduction; Basic concepts', Chapters 4 and 5 followed by appendices 1 through 4, which set the mathematical scene in a simple and understandable format. The link to a companion website extends the limit beyond those of purely printed texts. The site contains worked examples, multiple choice questions topics for discussions as well as the inclusion of a wide range of teaching tools both for tutors and those who prefer the self-taught route. Learning objectives at the start of each chapter plus the multiple choice questions will be a great help to the latter group.

While aspiring pharmacokineticists will find this book useful in developing their skills, it has in my opinion a wider audience, encompassing all those involved in drug development and drug use where pharmacokinetics plays a role – from the toxicologist to the clinical pharmacologist. The list includes pharmacists, biomedical and forensic scientists, pharmaceutical and formulation chemists, bioanalysts, clinical pharmacokineticists, translational scientists, patent lawyers, project leaders/managers, biomarker analysts and probably many more.

Chapter 1 provides a brief introduction to the basic essentials of chemistry and mathematics required to understand the rest of the book. Chapters 2 and 3 discuss drug disposition. While the role of cytochrome P450s in modifying the pharmacokinetics of both the parent drug and metabolite are well documented, our understanding of the role of transporters in this process continues to grow and is discussed with respect to the impact of interpolating their role within the complexity of drug excretion. It is commendable that the authors have seen fit to place topics such as transporters in their context; they are discussed in further detail in later Chapters such as 10, 11 and 12.

Aspects of pharmacokinetic modeling are introduced in Chapter 4 (single compartment models), while Chapter 5 expands the utility of multiple compartment and noncompartmental modeling. The concept of compartments and the value of noncompartmental modeling are discussed. Chapter 6, 'Kinetics of Metabolism and Excretion', explains the inter-relationship between parent drug and metabolite, summarized well in Figure 6.1, and the use of excretion studies to determine pharmacokinetic parameters.

Chapter 7 examines the uses of clearance in more detail, starting with *in vivo* assessment of clearance (metabolic stability) used in drug discovery studies to choose drug candidates and builds to discuss the *in vivo*–*in vitro* relationship. The chapter discusses aspects of hepatic clearance from a mathematical process to its clinical implications. These include the well-known and often misunderstood phenomenon of protein binding and its impact on hepatic

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clearance. Physiological modeling is elegantly summarized in Figure 7.6. The chapter segways nicely into the quantitation of the pharmacological relationships with drug plasma levels, PK/PD, (Chapter 8) and discusses the complex relationship between drug concentration and effect, especially where the effect may be regarded as indirect. Hysteresis plots are used to describe forms of dose–response relationship.

Chapter 9 on large molecules is a welcome addition to the field of pharmacokinetics and drug disposition, an area which provides new insights and interesting phenomena of kinetics and metabolism. The examples range from established biologicals like insulin and heparin to the newer synthetics such as trastuzumab and other monoclonal antibodies. The chapter might benefit from a glossary in its own right, but then it is an introduction to the topic and any further detail would merit a separate book.

Further consideration of PK/PD is to be found in Chapters 10–13, from the impact of pharmacogenetics to the impact of diseased states, not forgetting that well discussed and controversial area ‘side effects’. Chapter 10 discusses the role of pharmacogenetics and pharmacogenomics and the impact of these potential predictors of disease on the resulting phenotype. Effects on the expression of Phase I and Phase II enzymes are exemplified. The excellent use of tables and figures in summarizing these issues is exemplified in Table 10.2 and Figure 10.5, while Figure 10.6 graphically shows the impact transporters can have on drug exposure.

Chapter 11 discusses further factors that affect plasma concentrations; these are summarized in Box 11.1, which nicely cross references the chapters where they impact on the main topic of discussion. These include variation in individuals and what impact variables such as sex, age, life style, diseased states, pharmaceutical formulation, drug interaction and the like have on an individual’s pharmacokinetic parameters.

In Chapter 12, the attempt to integrate the physiological with the mathematical model is always to be commended, after all the data are generated to aid in the prevention or cure of disease. This is not simply an intellectual exercise in mathematical modeling. This is well exemplified in Chapter 12 by the effect of age and disease on drug disposition. It compiles and explains many potentially vague terminologies for which we assume we know the definition. Specifically definitions related to premature, neonatal, infant, child, adolescent and older adult (the assumption is that adults cover the range 16–65) although, I feel the term for younger adults 16–25 might be deemed useful as well. With an aging population consuming the greater part of the drug budget a better understanding/stratification of ‘older’ adults should be essential in better targeting of therapies. This is not a criticism of this book *per se* but a general observation that drug developers should not ignore. This is exemplified in the book by the impact diseases of old age such as kidney disease and function have on the kinetics of the drug.

Chapter 13 on the pharmacokinetic aspects of drug interactions and toxicity illustrates the need to be aware of drug-associated problems as well as their efficacy. Few, if any, drugs are without side effects. The chapter concentrates on the well-established areas of enzyme induction and inhibition caused by the impact of therapeutic agents on major areas of metabolism, chiefly the role of cytochrome P450s. This aspect of drug development is routinely evaluated in the early screening processes of drug discovery.

The final chapter examines the development of the topic and the historical perspective on bioanalytical analysis emphasizes the unpredictability of the utility of future technologies. Later, the chapter provides a tantalizing insight as to the future and discusses some of the growing areas of research including biomarkers a pivotal component in evaluating the PK/PD relationship. Personalized medicine is mentioned briefly as an area that is likely to expand as is increased development of monoclonal antibodies and other macromolecules.

Summary

This book has many innovations that make a welcome addition to the bookshelves of a wide range of pharmaceutical scientists. The effective use of figures and tables to summarize and clarify a wide range of issues is to be commended, as are the learning objectives at the start of the chapter coupled with the summary at the end providing a succinct way in understanding the objectives of the chapter and together with links to a website provides accessibility for all from the neophyte pharmacokineticist to the consultant physician. A book all in the Pharma industry should be aware of.

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