Handbook of Clinical Pharmacokinetics

Editors
Milo Gibaldi and *Laurie Prescott*

Section I	Pharmacokinetic Concepts
Section II	Physiological and Environmental Determinants of Drug Disposition
Section III	Effect of Disease States on Drug Disposition
Section IV	Therapeutic Drug Monitoring and Dosage Prediction

ADIS Health Science Press

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Preface

Pharmacokinetics is a vigorous well-established discipline. Some knowledge and understanding of its principles and application are important, not only as an aid toward safer and more effective drug therapy, but also in drug development, clinical studies of new drugs, therapeutic drug monitoring, clinical and 'traditional' pharmacology, and in toxicology. Progress in pharmacokinetic research has been facilitated by recent advances in drug analytical and computer technology, and a great deal of information is already available concerning the mathematical basis of pharmacokinetics and its application over a wide area.

For *clinical* pharmacokinetics, the lid of Pandora's box has been opened wide. The central role of this discipline in the definition of sensible, safe and effective dosage regimens, and in the problems of bioequivalence, individual variation in drug disposition and the relevance to drug response of factors such as age, disease and polypharmacy, is firmly established. However, the remarkable development and current sophistication of pharmacokinetics contrasts strangely with its limited impact on the manner in which drugs are actually used in clinical practice. Indeed, it is difficult to think of any other specialty with so much to offer that has such a poor record of application of existing knowledge to clinical medicine. Sadly, most patients are still given their drugs according to inflexible standard dosage regimens, often with quite illogical dosage intervals, and insufficient attention is given to the effects of important individual and pathophysiological factors known to influence drug kinetics and hence response. The great majority of serious adverse drug reactions occur not because the drugs themselves are particularly dangerous, but because they are used in a dangerous or illogical manner. It is true that considerable advances have been made in therapeutic drug monitoring, but this is no substitute for pharmacokinetic insight and rational thought on the part of the prescriber. Drug therapy could be virtually revolutionised by the widespread application of existing pharmacokinetic knowledge, and our patients would benefit enormously in terms of increased drug efficacy and safety. On the research side also, there are serious clinical shortcomings. It is almost always easier to measure drug concentrations than clinical drug effects. This is reflected in the success that the discipline has had in measuring drug concentrations in body fluids, and in studying the time course of such concentrations. Regretably, however, even allowing for methodological difficulties, the interrelationship between pharmacokinetic parameters and clinical drug effects has not been well addressed. Additionally, there is an enormous gap between predictions based on sound pharmacokinetic theory, or studies carried out under ideal conditions in young healthy volunteers, and the actual demonstration of their relevance in ill patients.

What is the remedy for this disturbing situation? The answer must lie in education and enlightenment, but there are problems here too. Clinical pharmacology has a very low priority in both undergraduate and postgraduate medical education in most coun-

tries, and in some schools medical degrees are awarded without adequate professional examination of the student's knowledge of the clinical use of drugs. To make matters worse, teachers, clinicians and even established research workers have had great difficulty in obtaining relevant clinical pharmacokinetic information, since most of it is scattered in a wide range of journals covering many different specialties.

To alleviate this latter problem, the journal 'Clinical Pharmacokinetics' was introduced in 1976. In bringing together a series of outstanding review articles in selected topics, and clinically relevant original research reports, it has been highly successful. Most of the articles are unique. They have been written by leading investigators in the field, and they bring together a wealth of priceless information which includes virtually all that is known of the clinically important aspects of pharmacokinetics in a particular area.

The demand for this valuable material is now such that selected articles have been reproduced in this volume. The most clinically relevant aspects of pharmacokinetics have been covered, and importantly the articles have been updated with additional references and amended by the authors as appropriate. We hope that the 'Handbook of Clinical Pharmacokinetics' will prove informative and stimulating to all whose work and study is directed towards better drug therapy, and in particular to teachers, students and those on the 'front line' who are directly involved in the prescribing of drugs. In this way it might eventually be possible to reverse the present situation where a vigorous pharmacokinetic tail is attempting to wag a seemingly unwilling clinical dog.

Finally, we must thank the authors for their splendid contributions. The work involved in producing and updating these classic review articles is formidable, and we are indebted to them.

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General Introduction

Everyone knows that few people read introductions. Those few who do probably belong to a distinctly different subset of the population than that other, much larger group of individuals who studiously pore over the 'letters to the editor'. Nevertheless, I will offer some observations, if only because I do believe that a tree that falls in a desolate forest does indeed make a sound, despite the absence of anyone to hear it.

As one among many who nurtured the development of pharmacokinetics, I am pleased and proud to report that it is thriving, perhaps not as a discipline, but as a valuable tool for experimental design and data evaluation. Examples abound of the applications of pharmacokinetics in basic biomedical research, in drug development studies and in the clinical arena.

In an important way pharmacokinetics has had considerable socioeconomic influence; one need only consider the issue of generic drugs that is presently under intense consideration in several countries. Application of the principles of pharmacokinetics permits us to arrive at rather precise conclusions regarding the bioequivalence of 2 or more products containing the same drug. We can make definitive, quantitative statements regarding the comparability of both the rate and extent of absorption of a drug from several dosage forms. Often, we can intelligently speculate as to the clinical significance of differences that may be found. An alternative to the pharmacokinetic approach of assessing the comparability of drug products is the clinical approach, an approach which is under scrutiny and debate in the USA today. Is there a need for the new manufacturer of a widely used drug to subject his product to the same or similar clinical trials that were required for approval of this drug? There appears to be little scientific basis for a positive response. Nevertheless, a view I have long held and share with others is that preclearance or preapproval by a regulatory or other appropriate group or agency should be required for all new drug products irrespective of the antiquity of or breadth of experience with the drug. Satisfactory performance of the new product in an appropriately designed human bioavailability study appears to be a reasonable criterion for such preclearance. This, the adherence by the new manufacturer to good manufacturing procedures and quality control standards, and the continued vigilance of the regulatory group to changes in formulation or process, would appear to guarantee to society that the drug products available may be used with confidence. This approach is certainly more costly than the system where preclearance is waived. On the other hand, it is far more economically, intellectually and ethically satisfactory than a system calling for repetition of clinical trials.

The first 3 contributions in this volume are appropriately concerned with bioavailability. The generic drug issue and the bioequivalence debate has embraced far more drugs than digoxin and phenytoin, but because of their clinical importance, widespread use, and relatively narrow therapeutic index in individual patients, these 2 drugs are apt examples.

Whether to take a drug with food or on an empty stomach is a rather old question, but the thought that such a decision could affect the clinical response to a drug by affecting bioavailability is a relatively recent insight.

As several contributions in this volume attest, we have learned a great deal about drug distribution during the past decade. Particular attention has been paid to plasma protein binding, blood flow to certain organs and tissues (most notably hepatic blood flow), tissue or extravascular binding, and the relationship between parameters used to describe distribution and those used to characterise elimination processes such as clearance and half-life. Despite the intense interest and considerable experimental effort, the clinical importance of disease-induced, drug-induced, or genetically derived differences in drug distribution is not obvious in most cases.

Our current quantitative understanding of drug distribution clearly reveals the pharmacokinetic consequences of changes in plasma protein binding. The many factors that may lead to reduced drug binding in the blood will, in the case of drugs that are essentially metabolised in the liver and display a low extraction ratio, produce an increase in the clearance and, often, a decrease in the half-life of the drug. This in turn leads to lower blood levels of drug for a given dosing regimen. However, unless the changes in binding are accompanied by changes in drug metabolism, these pharmacokinetic consequences are not of clinical interest. Under the conditions described, the decrease in total drug concentration in blood is not accompanied by a change in the free (unbound) drug concentration in blood; the latter is generally viewed to be a critical factor in determining the intensity of drug effect. Thus, rather remarkable changes in drug distribution may not require a change in drug treatment or dose.

Theory suggests that a decrease in the binding of a drug which is eliminated by hepatic metabolism and displays a high extraction ratio may result in an abnormally high free drug concentration in blood and lead to adverse effects. Such considerations should probably be kept in mind when using certain strong analgesics or tricyclic antidepressants, but clinical evidence to support this theory is not yet available.

Considering that in many cases almost all the drug in the body can be found to be bound in the extravascular space, and that changes in tissue binding can markedly affect drug distribution, the current interest in the influence of tissue binding on pharmacokinetics and clinical effect is not unexpected. On the other hand, there is virtually no experimental or clinical evidence to suggest that changes in extravascular binding influence the pharmacological effect of a drug or necessitate a change in dosage. Moreover, pharmacokinetic theory suggests that a change in extravascular binding will have no effect on the free drug concentration in blood. Distinct changes in half-life under these conditions may require the same daily dose to be given more or less frequently.

There is no question as to the clinical relevance of disease-induced changes in hepatic blood flow or cardiac output, to the efficacy of many drugs, particularly those which are eliminated by hepatic metabolism and display a high extraction ratio. In this case, theory is convincingly supported by substantial experimental and clinical evidence with such drugs as lignocaine (lidocaine). A significant decrease in cardiac output or hepatic blood flow may markedly decrease the clearance and increase the half-life of a drug and may require a considerable change in the dosing rate to avoid adverse effects. Strictly speaking, however, these clinical consequences are primarily related to a change in drug elimination rather than drug distribution.

The seemingly limited clinical significance of factors that influence drug distribution *per se* in no way detracts from the value of the experimental work that has been carried out in this context or from the theory that has been developed based on this work. These efforts, perhaps singularly, have radically changed the way we approach a pharmacokinetic analysis. Before these anatomical, physiological and pathophysiological insights, pharmacokinetic analysis, mathematical rigor aside, was little more than a descriptive exercise. This is no longer the case; in most instances a change in a pharmacokinetic parameter can be understood or

at least satisfactorily rationalised. Equally important, we can now almost always make a considered judgement as to whether such changes require a change in the drug treatment strategy.

The 2 contributions concerning hepatic blood flow perforce treat in considerable detail the hepatic elimination of drugs. Our quantitative understanding of the role the liver plays in drug metabolism, in health and disease, has increased sharply during the past decade. There are clear signs that it will increase still more in the decade to come. Other modes of drug elimination considered in this volume include renal and biliary excretion and lung metabolism.

Although the drug strategy in response to changes in renal function is probably better understood than for any other disease, including liver disease and cardiovascular disease, it is accurate to state that our quantitative understanding of the influence of pathophysiological and other factors on renal excretion, is not at the same level as may be found with respect to hepatic metabolism of drugs. A theory has recently been developed which considers the relationships among drug binding, renal blood flow and filtration, secretion and reabsorption processes, but experimental support is sparse.

It is equally accurate to state that relatively little progress has been made in applying the principles of pharmacokinetics to biliary excretion. The difficulty in accessing bile in man has resulted in the present situation where we are uncertain as to the importance of biliary excretion in the elimination of almost any particular drug. Our current understanding of and available information on biliary excretion, albeit circumscribed and limited, has permitted some applications of clinical pharmacokinetics. A particularly interesting example is the oral feeding of activated charcoal or non-absorbable resins to interrupt the enterohepatic cycle and thereby decrease the persistence and facilitate the removal of certain drugs and chemicals in the intoxicated patient.

The application of pharmacokinetic principles to lung metabolism of drug is really quite recent, but promises to be fruitful, perhaps much more fruitful than some of us anticipated only a few years ago when lung metabolism was thought to be largely a laboratory curiosity — except in the case of certain endogenous chemicals. That the anatomical position of the lungs results in first-pass metabolism of drugs after intravenous administration, similar to the role of the liver after oral administration of a drug, and that the metabolic clearance of drugs by the lungs is not restricted by blood flow but can, in fact, exceed cardiac output, suggest an important influence of the lung on the pharmacokinetics and clinical effects of at least certain drugs. Examination of non-linear processes and of factors that induce or inhibit drug-metabolising enzymes in the lung may prove to be of considerable interest.

The application of pharmacokinetics in the development and assessment of haemodialysis and haemoperfusion is obvious and its proven value comes as no surprise. Surely, clinicians can make much sharper judgements with the aid of pharmacokinetic principles and information as to the merits of employing these emergency measures to a particular patient intoxicated with a particular drug. Such judgements are necessary because such procedures are not benign. Pharmacokinetic theory has also proven useful in anephric patients who require routine dialysis. Such patients almost always require drug therapy, and in some cases additional doses need to be given to replace losses caused by the dialysis procedure.

Although most of the concepts developed in this volume have been the subject of 2 or more contributions, there are several that stand alone; they concern pharmacologically active metabolites, individual variability, and drug interactions. These concepts are of considerable clinical importance and are further elaborated on in subsequent volumes of this series. Prognostication is always risky, but it does seem likely that pharmacokinetics will prove to be a very valuable tool in developing our understanding of pharmacologically active metabolites, particularly reactive metabolites. There is a great deal of interest today in reactive metabolites. There is no doubt that these short-lived intermediaries play a principal role in the cellular necrosis induced by certain drugs in-

cluding paracetamol (acetaminophen) and isoniazid. Pharmacokinetic principles applied to this problem may be of great value in sorting out the role of competitive metabolic processes and overcoming the seemingly impossible analytical task of quantifying the reactive species. This application is likely to be of seminal importance in the development of pharmacokinetics.

In closing, I must acknowledge and pay tribute to the fine work of the individual contributors. The time and effort required to gather the information and prepare a review article is not inconsequential. Such efforts usually result in little recognition and 'ego-gratification'. Yet, when done well as in the present instance, comprehensive critical reviews are marvellous teaching instruments and serve as the cornerstone for future developments. They reach out to the uninitiated and to the young investigators and provoke the important question, the answer to which will permit us to take the next step. We thank you one and all.

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Bioavailability of Drugs:
The Digoxin Dilemma

D.J. Greenblatt, T.W. Smith and J. Koch-Weser

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Summary

The absorption of oral digoxin preparations has been a topic of much concern during the last 5 years. The completeness of digoxin absorption is proportional to the area under the serum concentration time curve and to the urinary excretion of digoxin after single doses. During chronic therapy the completeness of absorption is proportional to these values and also to the steady state serum concentration. Determination of absolute bioavailability of a given digoxin preparation requires a comparative study using intravenous digoxin as a standard.

Oral digoxin solutions are incompletely absorbed, but have biological availability greater than or equal to that of tablets. The absorption of digoxin tablets depends upon their dissolution rate which in turn is related to drug particle size. Digoxin tablets with small drug particles have rapid rates of dissolution and can be absorbed as completely as oral solutions. The bioavailability of digoxin from tablets can be influenced by changes in gastro-intestinal motility, malabsorption syndromes, and by co-administration of food or other drugs.

New regulations now insure that all marketed digoxin tablet preparations have satisfactory bioavailability. Problems with biological availability at present are unlikely to account for unexpected clinical results during digoxin therapy.

Five years ago Lindenbaum et al. (1971) reported that tablet preparations of digoxin containing the same amount of the drug produced very different digoxin concentrations in the serum of the same individuals. This observation led to much concern about the problem of bioavailability of drugs among clinicians, patients, drug manufacturers, clinical pharmacologists, legislators, drug regulatory agencies, and the lay public. All of these groups suddenly had to face the fact that the amount of drug absorbed from a given dosage form depends upon more than just the quantity of drug contained in that preparation.

Because the issue of digoxin absorption was 'newsworthy', and because a reliable method for quantitative assay of non-radioactive digoxin in body fluids was available (Smith et al., 1969), many investigators began to study this problem.

Undoubtedly the attention focused upon the bioavailability of digoxin has exceeded the clinical importance of the problem. Yet the digoxin interlude has served to emphasise that drug absorption and biological availability are an important and continuing concern in clinical therapeutics.

1. Drug Absorption and Bioavailability

1.1 Models of Drug Absorption

The absorption of exogenous substances from the gastro-intestinal tract is a complicated process involving many independent variables (Prescott, 1974; Gibaldi, 1971; Wagner, 1975). To facilitate understanding and analysis of drug absorption, pharmacokineticists have provided several oversimplified but useful mathematical models, two of which are considered below.

1.1.1 Two Compartments

The first important model of drug absorption involves modification of the two-compartment open system by annexation of an 'absorption site'. A drug dose (D) is introduced into the absorption site at time (t) zero (fig. 1). The drug passes into the central compartment with first-order kinetics, i.e., the absorption *rate* is proportional to the *concentration* of drug remaining at the site of absorption. The proportionality constant (k_a) is termed the absorption rate constant. Reversible drug distribution occurs between central and peripheral compartments, but irreversible drug elimination takes place only from the central compartment.

This model predicts that serum or central compartment drug concentrations (C_1) will be a triexponential function of time (t) after dosing:

$$C_1 = -(X_1 + X_2)e^{-k_a t} + X_1 e^{-\alpha t} + X_2 e^{-\beta t} \quad \text{(Eq. 1)}$$

A semilogarithmic plot of C_1 versus t may have three distinct components (fig. 2). The upswing or 'absorption' phase mainly represents the initial movement of drug from the absorption site into the central compartment. The peak value of C_1 occurs when the rate of drug entry from the absorption site into the central compartment equals the rate at which it is being removed by distribution and elimination. If absorption is rapid, a fast disappearance phase following the concen-

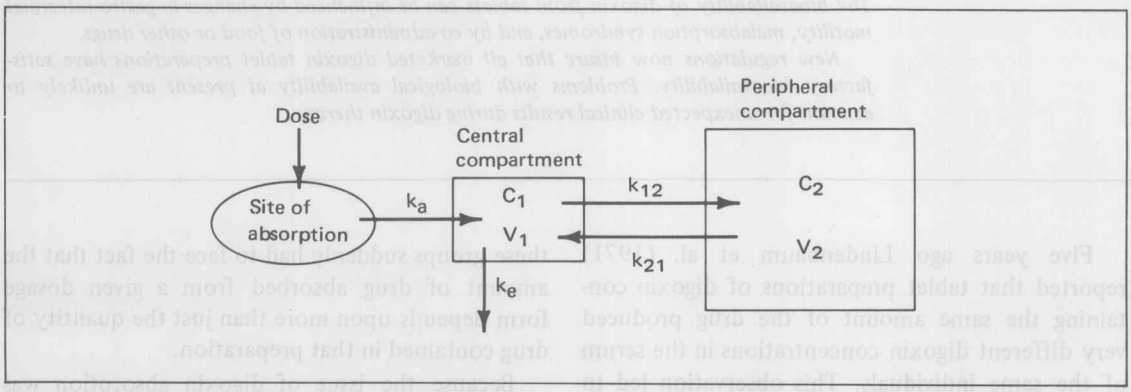

Fig. 1. Schematic representation of two-compartment open model. The dose is introduced into the site of absorption, from which it passes with first-order kinetics into the central compartment. C_1 and C_2 represent drug concentrations and V_1 and V_2 represent apparent volumes of central and peripheral compartments, respectively. k_{12} and k_{21} are first-order rate constants for drug transfer between central and peripheral compartments. k_a and k_e are first-order rate constants for drug absorption into and elimination from the central compartment.