Pharmacokinetics for the Non-Mathematical

D.W.A. Bourne, E.J. Triggs and M.J. Eadie

PHARMACOKINETICS

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by

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Preface

Several contemporary books on pharmacokinetics are available. Each has its particular merits, and each is most helpful in its own way. How can another book on the topic be justified?

Pharmacokinetic knowledge has had a very considerable influence on the thinking of recent pharmacy graduates. Unfortunately, it does not seem to have had an equal impact on the thinking of medical graduates. If the concepts of pharmacokinetics are valid, they should be a great help to those who are legally entitled to prescribe drugs. However, up to the present these concepts, if they have been accepted at all in medical practice, have often been received almost reluctantly and have sometimes been employed rather uncritically. Assuming that the concepts of pharmacokinetics are indeed valid, the relative failure, so far, of a potentially very useful tool to have a greater impact on contemporary medical thought and practice may have several explanations. For instance, the insights provided by applying pharmacokinetic principles in the clinical situation may have proved disturbing to the way of thinking of an older generation of clinicians. Additionally, the insights may have been seen merely as providing a rationale for existing and clinically satisfactory patterns of drug use (though accumulating experience suggests that pharmacokinetic insights often lead to altered and improved ways of using drugs). However, we suspect that the relative reluctance of the medical profession to make greater use of pharmacokinetic thinking has often stemmed from the way pharmacokinetic knowledge itself has been presented.

Some presentations of pharmacokinetics have been highly simplistic in terms of anatomy and physiology. Such presentations tend to be seen as rather unreal by clinicians, who have a well developed awareness of the structure and function of the human body and of biological variability. Other presentations are highly mathematical in their content. Medical graduates generally are not comfortable with mathematical, and particularly with algebraic, thinking. They tend to suspect that such highly mathematical approaches imply an unrealistic level of precision for any analysis of biological data. Further, the clinical examples often cited to convince the reader of the usefulness of their approach, frequently appear to the practising clinician as somewhat contrived, and implausible in the real life situation. They convey to the clinician's sense of physiological variation and human perversity, an impression of unreasonably precise and

perhaps potentially dangerous prediction. In general, pharmacokinetic texts have not provided a very realistic translation of certain kinetic concepts into anatomical and physiological terms. It may well be that such a translation is not yet possible. However, the very acknowledgement of this fact might make the clinician more sympathetic to the worth of pharmacokinetics, and might enhance the intellectual stature of the discipline in his eyes. Even for those clinicians who sense the potential practical utility of pharmacokinetics, and wish to carry out pharmacokinetic analysis on their own data, there is the problem of finding adequate information in a single book about 'how to do it' in a form which they can use immediately. It is almost as though there has been a conspiracy to tantalize the clinician with the prospect of the wondrous data he might be able to obtain if he had access to a large computer and if someone else already had the appropriate program running on it, but to conceal from him how he could do his own pharmacokinetics fairly simply and cheaply, working at a level of exactness consistent with the accuracy of the data he is likely to obtain from his patients.

In the present book we have attempted to overcome to some extent what we have seen as shortcomings in the way the subject of pharmacokinetics has often been presented. We have tried to restrict algebra and mathematics to a minimum and have not always attempted to develop a logical consecutive mathematical system of reasoning. Rather, we have preferred at times to ask the reader to take certain mathematical statements on trust (but telling him when this is done). Where possible, mathematical ideas have been expressed in the form of graphs, since most medical graduates seem more comfortable interpreting graphs than equations. Throughout the book we have attempted a critical correlation of pharmacokinetic concepts with the level of anatomical and physiological knowledge one might expect of a medical graduate, and we have tried not to let the interpretation of pharmacokinetic ideas and the predictions drawn from them outrun the clinician's experience of what is likely to occur in a diseased state. We have been at some pains to distinguish that which is predicted from that which is established by observation. At the same time we have attempted to show how the predictions may be put to the test and, if proved correct, may later come to alter and enhance clinical practice. We have tried to show the clinician how he might carry out his own pharmacokinetic analyses of data with simple techniques using graph paper and hand-held calculators. In addition, bearing in mind the increasing availability of comparatively cheap 'home' microcomputers, we have also attempted to provide the clinician with access to 'software' that will allow him to carry out his own pharmacokinetic calculation at a quite reasonable level of sophistication and with a precision in keeping with the precision of the data he is likely to be able to collect from his patients (if he has access to a laboratory which can measure drugs at the concentrations at which they occur in clinical practice).

Thus we have tried to write a short, reasonably critical book on pharmacokinetics directed towards the interests and needs of medical students and medical graduates. Possibly the book may also provide some insights of

value for students of pharmacy, dentistry, veterinary science and pharmacology. We hope it will lead some who practise medicine, or will soon practise it, to a heightened awareness of how pharmacokinetic thinking may make drug therapy more rational, more effective and safer.

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The rationale and use of pharmacokinetics

In nearly all instances drugs appear to produce their effects in man and other animals by forming bonds with various endogenous biological molecules. This bonding then sets in train further chemical events which find expression as the pharmacological action (or actions) of the drug. The processes of drug–receptor bonding, and the subsequent molecular events which transduce this interaction into the discernable 'actions' of the drug, are embraced by the term *pharmacodynamics*. In contrast, the term *pharmacokinetics* refers to those processes by which the drug enters the body, is moved around within the body (and thus reaches its sites of action), and is eliminated from the body (thus terminating any action it has in its own right). Thus pharmacokinetics embraces the (1) absorption, (2) distribution, and (3) elimination (by metabolic biotransformation and/or excretion of the unchanged compound) of drugs, but not their action. Distribution and elimination are sometimes referred to collectively in the single term 'disposition'. The word *pharmacokinetics* is often used in a more restricted sense than that above. It then refers only to the mathematical analysis of the processes of drug absorption, distribution and elimination. It is in this latter sense that the word *pharmacokinetics* will be used from here on in this book.

If such mathematical procedures are to prove clinically relevant, at the very least they should be able to assist the clinician in his use of drugs. The clinician's chief purpose in using drugs is to achieve the therapeutic benefit desired without producing an unacceptable level of unwanted effects. The clinician's concern thus lies primarily in the pharmacodynamics of the drugs he uses. The question then arises: how can pharmacokinetics assist the clinician in his concern with pharmacodynamic matters?

Depending on the drug and the circumstances under consideration, there may be one or more answers to this question. The most widely applicable answer is the claim that pharmacokinetic knowledge helps the clinician predict the likely time course and extent of the effect of a given dose of a drug in a given individual. This answer is valid even in those occasional instances when the action of the drug in question can be measured immedi-

ately and conveniently, e.g. the regulation of heart rate in cardiac arrhythmia, the control of blood glucose concentration in diabetes mellitus, the decrease of prothrombin activity in thromboembolic vascular disease and the reduction of airways resistance in asthma. Even in these circumstances it is still useful to the clinician to know approximately when the maximum effect of a drug dose may be expected. He may then ascertain whether, at that time, benefit still outweighs undesired effects without the necessity of carrying out sequential measurements of the relevant drug actions. It is also helpful for the clinician to know in advance when the effect of a given dose of a drug is likely to cease, so that a second dose may be given at an appropriate time.

A second answer arises in relation to drugs whose actions are not readily quantified and/or have clinical effects which may not be obvious until some time after the drug initiates its biochemical effects. Thus in antimicrobial chemotherapy a dose of an antibiotic may kill or inactivate the responsible organisms within a few hours. However, the clinician may not be sure that he has prescribed adequate therapy for another 2 or 3 days, until resolution of various aspects of the inflammatory process produced by the infection has had time to become clinically apparent. In such a situation knowledge of the minimum inhibitory concentration for the chemotherapeutic agent towards the causative micro-organism, and use of pharmacokinetic information concerning the agent's disposition will enable calculation of the likely range of concentrations of the agent that will be achieved in the relevant body fluid. This knowledge can give the clinician reasonable grounds for expecting that he has prescribed adequate therapy, even at the outset of treatment. Drugs are sometimes given to prevent disorders which occur episodically, at irregular and often unpredictable intervals (as in epilepsy or migraine). In such cases if the relation between drug effects and drug concentrations in accessible body fluids is known, pharmacokinetic calculations can be used to determine whether a potentially suitable drug dosage is being used, without having to await the clinical response revealed by the passage of time.

How is it possible for pharmacokinetic information to be used in these ways to, as it were, anticipate the course of a drug's pharmacodynamics? The answer lies in considering events at the interface between pharmacokinetics and pharmacodynamics, i.e. the binding of drug molecules to receptors, and in considering the way in which drug molecules become distributed through the body.

DRUG–RECEPTOR INTERACTIONS

Receptor events

The term 'receptor' has sometimes been applied to all tissue molecules which form chemical bonds with drug molecules. Here the term 'receptor' is used more restrictively. It refers only to those binding sites at which the bonding leads to further chemical events which become manifest as pharmacological actions of the drug, both desired and undesired. The word

'acceptor' may be used to refer to those binding sites at which the bonding leads to no pharmacological effect.

Reversible bonding

Bonding between drug and receptor is, in most instances, non-covalent (i.e. it is electrostatic, involving ionic, dipole–dipole or hydrogen bonding). Such bonding tends to be readily reversible under physiological conditions. In such instances, the degree of drug action generally appears proportionate to the number of receptor molecules bonded to drug molecules at any given time. This is the basis of the receptor 'occupancy' hypothesis, though in relation to this hypothesis quantitative effects of the bonding may be influenced by some receptors being in an inactive state when drug molecules bond to them. In contrast to this situation, drug action occasionally appears proportionate to the rate at which drug molecules bond to receptors. This rate is determined by the rate at which previously formed drug–receptor combinations break down, leaving receptors available for further bonding to other drug molecules. In either situation the concentration of drug molecules in the region of receptors (in the so-called 'biophase') is a determinant of the rate and number of drug–receptor bondings. Drug concentration in the biophase thus tends to determine quantitative aspects of drug action. If one could measure drug concentrations in the biophase one would have a measure of drug effect, even if that effect could not readily be measured directly and even if the effect was not immediately detectable, because of delay in the translation of drug–receptor bonding into discernible actions.

There is considerable contemporary interest in the study of drug–receptor interactions. It seems likely that this study will throw considerable additional light on quantitative considerations at the drug–receptor interface. The above simplistic account of drug–receptor events may need substantial modification in the future. Further, it may be wise to sound a note of caution about the interpretation of some of the earlier drug binding studies. Contemporary biochemical methodology makes it comparatively easy to demonstrate bonding between drug molecules and tissue molecules. This demonstration is not proof that the binding sites are necessarily receptor sites, if the word 'receptor' is used restrictively to refer to tissue molecules where bonding is ultimately transduced into pharmacological activity. Sometimes one can be reasonably sure that the binding of a drug to its actual receptors has been studied, because the number of bindings was directly proportional to a biochemical change consequent on the binding, and this biochemical change is known to mediate the action of the drug, e.g. formation of cyclic adenosine monophosphate following the attachment of noradrenaline to certain types of β-adrenoceptors. Sometimes the evidence that a drug has bound to its receptors is less direct, and therefore less compelling. Thus the binding of a series of congeneric drug molecules may be shown to parallel the known potencies of these drugs towards the actions mediated by the receptor studied. Unfortunately at times in the past, it appears to have been assumed that any tissue molecule to which a drug

binds is necessarily a receptor for that drug. Until quantitative aspects of drug–receptor bonding have been subjected to further critical experimental study it may be unwise to attempt to refine interpretation of events at the pharmacokinetic–pharmacodynamic interface. One as yet has little secure basis for going beyond the generalization that drug effect is likely to prove proportionate to drug concentration in the biophase. Even here there should be the proviso that, as drug concentration in the biophase rises, there must come a stage at which maximum receptor occupancy (and maximum drug effect) occurs, since there must be a finite number of receptors in the body. There is now reasonably good evidence that receptor numbers in a given organism may not be static, but may alter as a consequence of physiological factors or as a result of drug–receptor bonding itself. This alteration may change the biophase drug concentration–pharmacological response relationship, particularly at higher drug concentrations, and thus vary the upper limits of the pharmacological response.

The expected relationship between biophase drug concentration and biological effect for a reversibly-bonded drug might be expected to resem-

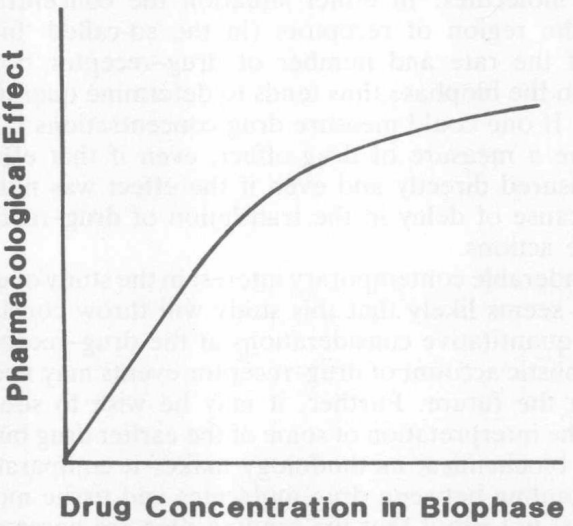

Figure 1.1 Relation between pharmacological effect and drug concentration in biophase for a reversibly bound drug

ble that shown in Figure 1.1. A similar appearance should also apply if there were a rate-limiting biochemical step at some stage between drug–receptor binding and the appearance of the pharmacological action of the drug, though here, of course, it would not be the drug–receptor bonding that set the limit to the pharmacological effect.

Irreversible bonding

In the previous section we have been considering drug–receptor bonding when the bonding is readily reversible under physiological conditions. But what happens when the bonding is covalent, and essentially irreversible

under physiological circumstances unless there is an enzyme present which can catalyse bond cleavage? When drug concentration rises in the biophase, previously unoccupied receptors will become occupied by drug molecules, and drug action will increase in extent. When drug concentration in the biophase subsequently falls, unlike the situation in reversible bonding, receptors already occupied will not become vacant. Therefore drug action will not diminish. Drug action will continue, even when no drug remains in the biophase, until the occupied receptors are themselves degraded and replaced, or until some subsequent stage in the biochemical events that transduce the drug–receptor bonding into the drug's action is interrupted. The pharmacokinetics of an irreversibly-bound drug such as the monoamine oxidase inhibitor phenelzine (i.e. its absorption, distribution and elimination) can be interpreted mathematically, and its concentrations elsewhere can be related to drug concentration in the biophase. However, the biophase concentrations of irreversibly-bound drugs show no simple consistent

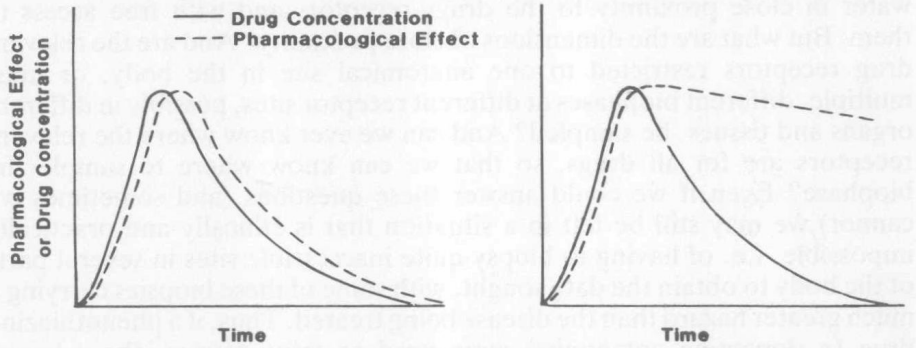

Figure 1.2 Time courses of drug concentrations (continuous line) and pharmacological effects (broken lines) for reversibly bound (left half) and irreversibly bound (right half) drugs

direct relationship to biological effect (Figure 1.2). This is unlike the situation for the drug with reversible bonding to receptors (for which drug concentration in the biophase tends to be proportionate to the pharmacological effect of the drug, at least over a certain concentration range). Given the present state of knowledge it would be very difficult to determine any sort of simple exact mathematical equivalence between biophase concentrations of irreversibly-bound drugs and pharmacological effects. Drug effects are the clinician's prime concern. Therefore, pharmacokinetics has less to offer the clinician in the case of irreversibly-bound drugs than in the much more common situation of reversible drug–receptor bonding. Admittedly, if one knew the time course of the degradation of drug–receptor complexes, and the rate of new receptor synthesis, it should be possible to define a mathematical relationship between biophase drug concentration and biological effect for irreversibly-bound drugs. However, the requisite knowledge is not yet available, and even if it were the mathematics involved might prove rather formidable, and perhaps too complex to be used in practice.

Drug concentrations in the biophase

Pharmacokinetics is made a practical possibility by the ability to measure

drugs at the concentrations at which they are found in the human body during the course of therapy. Without the ability to carry out such concentration measurements pharmacokinetics could be only a theoretical exercise. It might be illuminating conceptually, but it would be difficult to apply in the concrete situation of the individual patient prescribed a drug.

The argument has been developed above for measuring drug concentration in the biophase as an often valid indication of the likely degree of pharmacological effect produced by a drug. That may well be so, but is it practicable to measure drug concentration in the biophase? Analytical methodology has achieved sufficient sophistication for it to be nearly always possible to measure drugs with adequate specificity and sensitivity at the concentrations at which they occur in the biophase. Therefore the answer to the question posed above would usually be yes, so long as the anatomical location of the biophase was known, and samples could be collected from this locale. Presumably the biophase would comprise that portion of body water in close proximity to the drugs receptors and with free access to them. But what are the dimensions of close proximity? And are the relevant drug receptors restricted to one anatomical site in the body, or must multiple, different biophases at different receptor sites, possibly in different organs and tissues, be sampled? And can we ever know where the relevant receptors are for all drugs, so that we can know where to sample the biophase? Even if we could answer these questions (and sometimes we cannot) we may still be left in a situation that is ethically and practically impossible, i.e. of having to biopsy quite inaccessible sites in several parts of the body to obtain the data sought, with some of these biopsies carrying a much greater hazard than the disease being treated. Thus, if a phenothiazine drug (a dopamine antagonist) were used to treat nausea, the relevant biophase would be that of the chemoreceptor trigger zone of the medulla oblongata. Obtaining a sample from this region would require major neurosurgery and would carry quite prohibitive dangers. And since one might also be concerned about the extrapyramidal unwanted effects of the therapy, the biophase in the corpus striatum should also be studied. Again such sampling would involve quite unacceptable hazards.

Except in rare instances, it is not practicable to measure drug concentration in the biophase(s), simply because it would be completely unreasonable to attempt to sample this portion of body water. Does the possibility of applying pharmacokinetics thus founder on this simple issue of practicality and ethics? There is, in fact, a solution to the dilemma, a solution based on knowledge of how a drug becomes distributed throughout the body. This solution resolves the ethical problem and offers an advantage of simplicity. However, it sacrifices something of the precision that might accrue from measurements made on the drug in its actual biophase, or biophases.

DRUG DISTRIBUTION IN THE BODY

Spatial pattern

Drug molecules are rarely moved through cell membranes by active or

facilitated transport. Much more often their movement within the body occurs by virtue of passive transfer along concentration gradients. Therefore in nearly all instances the spatial pattern of drug distribution within the body tends to be determined by (1) drug solubility in various body fluids and in the component molecules of tissues, particularly the molecules in cell membranes, (2) bonding of drug molecules to various molecules (not only to receptor molecules) in body fluids and in cell membranes, and (3) movement of body fluids, particularly the blood and interstitial fluids.

Drug distribution within the body at a particular moment can be schematized as a series of concentration equilibria (Figure 1.3).

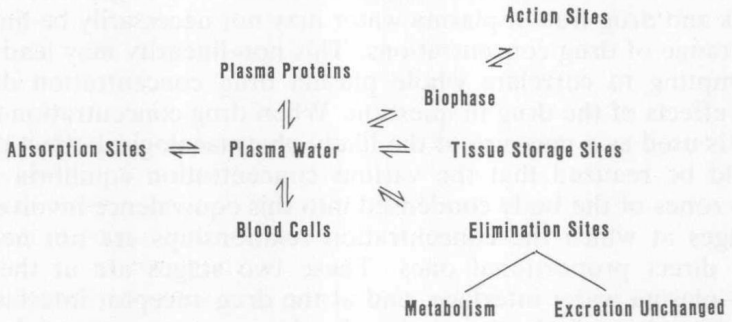

Figure 1.3 Scheme of the equilibria involved in drug distribution within the body

In the interests of simplicity the scheme in Figure 1.3 may not have made certain possibilities as clear as it might. Thus for the one drug there may be multiple different receptor sites, and a different biophase for each type of receptor site, and some (or all) of the biophases may be part of interstitial water (or even of plasma water). The scheme indicates that, at any moment, drug concentration in the biophase (or biophases) is related, through one or more concentration equilibria, to drug concentration in plasma (and the latter is nearly always readily measurable). This comes about as follows. In most instances, drug in the biophase(s) will be separated from drug in plasma water by one or more lipid membranes; transfer of drug molecules through these membranes is almost always a passive process, the rate of which is proportionate to the drug concentration gradient. Therefore, drug concentration in plasma water should vary in proportion to drug concentrations in the various biophases. Even if there are multiple biophases in the body, though the concentration equilibrium between each biophase and plasma water may differ from the next, the concentration of the drug in plasma water throughout the body (a comparatively uniform concentration because of intravascular mixing and the rapidity of the circulation) will still provide a single common measure of (the different) drug concentrations in the biophases. Therefore, drug concentration in plasma water provides an index of all the effects of a given drug (so long as the drug is one that binds reversibly to receptors, as most drugs do, and all available receptor sites are not saturated with drug). Thus measurement

of drug concentration in plasma water yields information about the likely quantitative effects of reversibly bound drugs.

In practice it is often rather cumbersome to measure drug concentrations in plasma water, because of the laboratory processes (dialysis, ultrafiltration) involved in separating plasma water from plasma proteins. Therefore, in view of the further reversible concentration equilibria between drug molecules in plasma water, and those bound to plasma proteins (Figure 1.3), drug concentrations are usually measured in whole plasma. Whole plasma drug concentrations are taken as a measure of biophase drug concentrations. However, it should be realized that plasma proteins also have a finite number of sites to which drug molecules can bind. Consequently, the relationship between concentrations of drug bound to plasma proteins and drug free in plasma water may not necessarily be linear over a wide range of drug concentrations. This non-linearity may lead to error in attempting to correlate whole plasma drug concentration data with clinical effects of the drug in question. When drug concentration in whole plasma is used as a measure of the likely pharmacological effect of a drug it should be realized that the various concentration equilibria between various zones of the body condensed into this equivalence involve at least two stages at which the concentration relationships are not necessarily simple, direct proportional ones. These two stages are at the plasma protein–plasma water interface, and at the drug–receptor interface. With this qualification, whole plasma drug levels at a given moment do provide a measure of the pharmacological effect of a drug that is reversibly bound to its receptors and which is not subject to active or facilitated transport through biological membranes.

Quantitative aspects of drug distribution may change with time after dose intake, largely as a result of the ongoing processes of drug absorption and drug elimination. Thus far, drug distribution has been dealt with as though it were a static, unchanging event. The time factor in drug distribution should now be considered, for pharmacokinetics involves not merely the interpretation of drug concentrations within the body at a particular moment, but also the interpretation of their time courses.

Temporal pattern

After a drug dose is given by any route other than the intravenous one, the drug concentration in plasma rises until the time when the amount of drug being absorbed in unit time falls below the amount being eliminated over the same period. After this time plasma drug concentration falls progressively until the next drug dose is taken. Drug concentrations in the biophase will tend to follow the time course of drug concentrations in plasma, but there may be an appreciable time lag between the two. This lag time is determined by the rate and extent of the circulation to various regions of the body, the rates of transfer of drug molecules across the various biological membranes intervening between the circulation and the biophase and by binding equilibria rates. This delay may distort the quantitative constancy of the static relationship between plasma and bio-

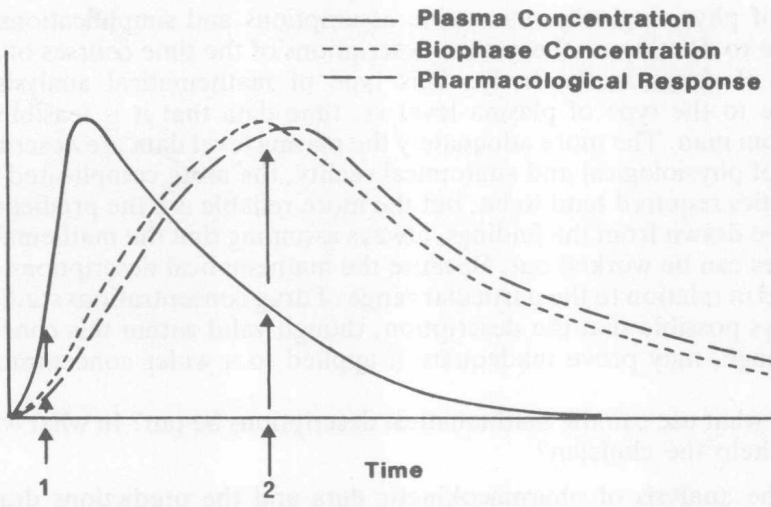

Figure 1.4 Time course of drug concentrations in plasma and the biophase after a drug dose. At times 1 and 2 the same plasma drug concentrations are associated with very different drug concentrations in the biophase and with different biological effects. However, in the postdistribution phase (well after 2), when the drug has achieved its definitive distribution throughout the body, the ratio between plasma and biophase drug concentrations becomes relatively constant until the next dose is taken

phase drug concentrations discussed in the preceding section. As indicated in the legend to Figure 1.4, after enough time has elapsed following a drug dose for drug distribution to have attained its definitive pattern, the ratio between plasma and biophase drug concentrations should remain reasonably constant until the next dose is given. During the earlier distributional phase there may be a higher ratio of plasma to biophase drug concentrations, relative to the postdistributive value of this ratio. This higher value is a consequence of the more restricted but increasing extent of distribution of the drug in the body as the distribution phase proceeds.

Thus the arguments developed relating plasma drug concentration to pharmacological effect should be subjected to the caveat that they apply more closely after a drug has achieved its final distribution pattern in the body.

THE POSSIBILITY OF MATHEMATICAL PHARMACOKINETICS AND ITS VALUE

So far we have developed a semiquantitative argument. This argument attempts to show that, with the presence of a drug in the body, for the majority of drugs (those that appear to bind reversibly to their receptors and are transported passively across plasma membranes) there is a relationship, though not necessarily a constant proportionality, between plasma drug level and potential pharmacological effect of the drug. Is it feasible to define such a relationship with greater mathematical precision? Would such a mathematical description have any practical value?

It will be shown in subsequent chapters that, by virtue of making a

number of physiologically reasonable assumptions and simplifications, it is possible to develop mathematical descriptions of the time courses of the presence of drugs in the body. This type of mathematical analysis is applicable to the type of plasma level vs. time data that it is feasible to collect from man. The more adequately the plasma level data are described in terms of physiological and anatomical reality, the more complicated the mathematics required tend to be, but the more reliable are the predictions that can be drawn from the findings, always assuming that the mathematics themselves can be worked out. Because the mathematical descriptions are developed in relation to the particular range of drug concentrations studied, it is always possible that the description, though valid within this concentration range, may prove inadequate if applied to a wider concentration range.

And to what use can the mathematical descriptions be put? In what ways can they help the clinician?

(1) The analysis of pharmacokinetic data and the predictions drawn from this analysis can provide additional insights into what appears to happen to drugs within the body.

(2) So long as the range of plasma drug concentrations associated with a particular pharmacological effect is known, pharmacokinetic data drawn from the population (and preferably, if possible, from the individual in question) can be applied to the individual to give the prescriber a better basis for determining:
   (a) the appropriate drug dose to gain a desired effect,
   (b) the appropriate dosage interval, if the drug is to be given in repeated dosage,
   (c) the likely time course of the drug's biological effect after each dose, including the time when the maximum effect can be expected, and the time when the effect should have worn off.

   By use of this information therapeutic regimes may be rationalized, often simplified and yet made more effective.

(3) Pharmacokinetic awareness may assist in the recognition and interpretation of the mechanism of drug–drug interactions when more than one drug is taken by a patient, and may help in the recognition of possible adverse effects of drugs.

(4) The numerical values of pharmacokinetic data allow a great deal of information about drugs to be contained and stored in a very concise form. The values of standard pharmacokinetic parameters become, in effect, a code which, if understood, gives the clinician access to drug information stored in a readily portable form. He can then use this information for the purposes set down immediately above (1, 2 and 3).

THE VALIDITY OF PHARMACOKINETICS

Pharmacokinetics has had a considerable effect in enhancing our understanding of what happens to drugs within the body, and has opened a way