MATHEMATICAL MODELLING IN PHARMACOLOGY

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Introduction

The primary objective of Clinical Pharmacology is the effective treatment of *human* disease by drug therapy. The associated problem is the design of *rational* drug administration programs. The resolution of the problem lies in the convergence of many disciplines ranging from Biochemistry and Physiology to Statistics and (more recently) Mathematics. The response of humans to drugs displays considerable variability. Thus, statistical techniques have played an important role in drug administration. Advances in techniques of measurement during the past ten years have made possible the study and reduction of variability by using mathematical (and numerical) modelling.

Classical Basis of Drug Therapy

The basic concepts in drug administration are

(i) Dose: A single dose is adequate in some circumstances. In other cases it may be necessary to give a sequence of doses, for example, until a disease has been cured or on an extended basis if a disease can only be contained.

(ii) Response or Pharmacologic effect: There is normally a desired minimum therapeutic effect. Drugs usually have multiple effects, some of which may be toxic (causing,e.g. nausea, vomiting) or lethal.

The problem is to understand the relationship between dose and response. The classical approach is statistical in nature. Consider the single dose administration program as

an illustration. Each member of a sample of the population is given a dose and the fractions of the sample in whom a therapeutic response and in whom a toxic response occurs is measured. The cumulative frequency distribution of response typically (there are well-known exceptions [1]) has the appearance shown in Figure 1.

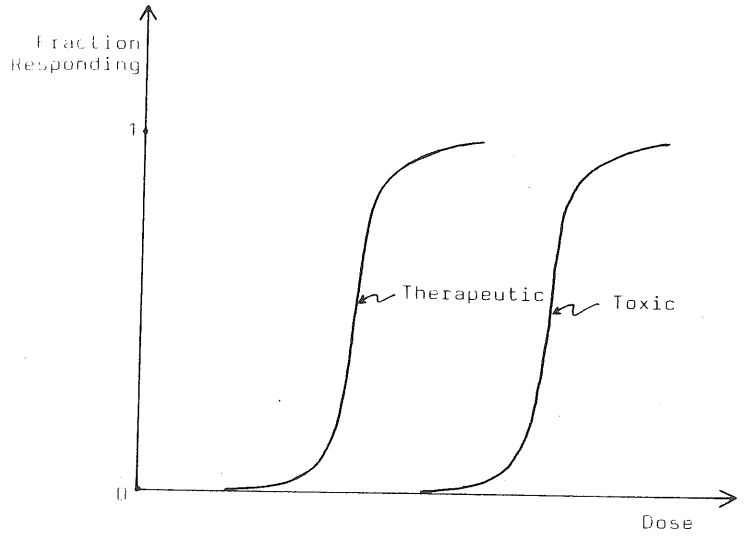

FIGURE 1

The dose at which n per cent of the sample shows a therapeutic (toxic) response is commonly denoted by EDn (resp. TDn). If ED99 is significantly less than TD1 the drug is considered to be both safe and effective. However, if TD1 > ED99 it is not possible to find a dose which will be both safe and therapeutically effective for the whole population. Unfortunately, many important drugs fall into the latter category and it thus becomes necessary to understand the nature of the variability in order to safely and effectively treat many diseases.

Physiological and Biochemical Considerations

All theories of drug action start from the premise that a drug exerts its effect by interacting chemically with certain molecules, called *receptors*, in the body [1]. The location of the receptors depends on the drug. The identification of receptors is now a major research area in Pharmacology [2,3]. Implicit in such theories is the view that, in order to understand the nature of response to a drug, the *distribution* of the drug throughout the body must be known or inferred. Further, if the interaction is chemical, the *concentration* of the drug at receptor sites will be the key quantity which determines the magnitude of the response.

Drugs are commonly introduced into the body by the oral and intravenous routes (there are many other routes). In the intravenous case the drug is injected directly into the bloodstream. Orally-administered drugs may be absorded into the blood from any part of the gastro-intestinal tract (mouth-stomach - small intestine - large intestine - rectum). The main site of absorption is the small intestine. In each case the introduction of drug into the blood is important since it transports the drug throughout the body. The other fluid contents of the body are also important for the distribution of drug. Body fluids account for 60% of body weight. The volume of the blood is about 5 litres of which 3 litres consists of *plasma water* and 2 litres is contained in blood cells. A further 26 litres is contained in other cells of the body (*intracellular*) and 10 litres occupies the space between cells (*intercellular*). Most drugs, once in plasma, will distribute throughout the extracellular fluid. The rate of drug penetration into intracellular fluid depends on the degree of perfusion of the various tissues (groups of similar cells) by blood. In addition to convective transport by blood, distribution of drug occurs by various diffusion processes. The known processes are: neutral diffusion in accordance with Fick's law [4], electrodiffusion in accordance with the Nernst-Planck law [5], facilitated diffusion [6] and active transport

[6]. The following list gives a rough categorization of tissue on the basis of *vascularity* (perfusion by blood):

(i) A highly perfused tissue group; blood cells, heart, lung, liver, kidney, brain and spinal cord.

(ii) A poorly perfused tissue group; muscle and skin.

(iii) A fat group; includes bone marrow.

(iv) A negligibly perfused group; bone, teeth, ligaments, cartilage and hair.

Drugs are removed from the body by the processes of *excretion* and *biotransformation*. The most important vehicle for the excretion of drugs is the kidney. (Volatile gases, which are mainly excreted by the lung, are not considered in this article.) The *renal* (kidney) elimination process is complex and involves three processes: glomerular filtration (driven by a pressure gradient from plasma to urine), tubular reabsorption (electrodiffusion of drug from urine back into plasma) and tubular secretion (removal of drug from plasma by active transport). The relative significance of each process is drug-dependent. Biotransformation corresponds to the de-activation of drug by chemical transformation. Such chemical reactions occur mainly in the liver and are enzyme-mediated. The transformed inactive drug (metabolite) is eliminated by the kidneys [7].

Mathematical Modelling - Pharmacokinetics

The aim of the receptor-theories of drug action is two-fold:

(i) to obtain an understanding of the relationship between dose and response in a manner that disposes of inter-individual variability;

(ii) to enable the design of rational drug-administration programs.

Since the effect is now postulated to depend on the *concentration* of drug at receptor sites, the variability must be due to physiological factors which cause a given dose to give rise to different concentrations at the receptor sites of different individuals. Thus, it would seem that prospective mathematical models would have to be able to describe the evolution of drug concentration in the body and also to describe the relationship between concentration at receptor sites (usually unknown, at present) and pharmacologic effect. The approach that has been taken by pharmacologists is pragmatic. Physiological modelling would be a complex process [4,8] and it would probably be quite difficult to develop simple whole body models which could easily be used in clinical practice. The simplest approach would be to administer a drug and see what happens. There is, however, a severe limitation on the nature of measurements that can, ethically, be made at the present time. The measurement of drug levels is limited to those in blood plasma and urine. The concentrations can be very small (of the order of nanograms/millilitre) and are difficult to measure. Considerable effort has been expended on the development of accurate techniques over the past ten years [9].

Compartment Models

Consider the following experiment. A dose of drug is rapidly injected intravenously and plasma concentrations are measured at a number of later times. The results are surprisingly simple. For many drugs, the plasma concentration decays exponentially. More precisely, a decaying exponential seems to fit the data. For other drugs, a linear combination of decaying exponentials will fit the data. The curves are usually fitted using non-linear least square techniques [10]. It could certainly be argued that these results have no great physiological significance. For example, Muntz's theorem [11] tells us that the set of exponentials $\{e^{-\lambda_n t}, 0 < \lambda_1 < \lambda_2 < \ldots$ $\ldots, \Sigma\lambda_n^{-1} = \infty\}$ is complete on $L^2(0,\infty)$. However, continuing in a spirit of pragmatism, we could speculate that these exponentials could correspond to eigenfunctions of a linear-system of differential equations

$$\frac{dv}{dt} = Av$$

where v is an n-vector, A is an nxn matrix and n is the number of exponentials. Then the plasma concentration would be one component of a vector. On the basis of this model, pharmacologists consider the body to consist of a number of *compartments* between which drug can transfer reversibly. A compartment does not necessarily correspond to any anatomically or physiologically identifiable part of the body.

The One-Compartment Model

In this case the model equation is

$$\frac{dc}{dt} = -kc \ , \ t > 0 \qquad (1)$$

where t is time since administration (assumed to be instantaneous) and c is plasma concentration of drug. The time taken for the drug concentration to decrease by a factor of one-half is known as the drug half-life($= \ln 2/k$). Typical half-lives range from hours to days, so that injection times of the order of a few minutes may be taken to be instantaneous. Both c(0), the initial plasma concentration and k are found from the exponential curve fit. The known initial quantity is the amount of drug administered, D. If the drug were confined to plasma then we would expect

$$V = \frac{D}{c(0)} \simeq 3 \text{ litres (the volume of plasma-water)}$$

The quantity, V, bears the unfortunate name of 'volume of distribution' of the drug. Observed values of V can be several orders of magnitude greater than 3. For example, the value of V for quinacrine (an anti-malarial drug with a half-life of 10 days) is of the order of 10^4 litres. In general, only a small fraction of drug is in plasma. The transfer of

drug from plasma to the rest of the body must be rapid in order for the early concentration in plasma to be so small.

This simple model has contributed to the understanding of dose-response variability. When plasma levels of individuals given the same dose are measured it is found that both c(0) and k are variable. The value of k can show considerable variation which is thought to be related to genetic factors. It can also vary significantly with age (e.g. underdeveloped elimination processes in newborn babies), with temperature (which can be raised or depressed in illness and can influence biotransformation processes) and with other factors [7]. Thus, we have a possible explanation of variability in response to a fixed dose. Space does not permit a discussion of the various receptor theories of concentration-effect [1,12]. If the relationship between plasma concentration and that in other parts of the body were simple it might be possible to find a relationship between plasma concentration and effect. Pharmacologists have made the simplest assumption that the concentration in other parts of the body is *proportional* to that in plasma and have gone on to seek relationships between plasma concentration and effect. Relationships of this type which also conform to receptor-theory have been found [13,14].

The model has also been applied to the design of therapeutic drug administration programs. Of the many possible routes for administration we consider only the oral and intravenous cases. Some drugs (e.g. analgesics, hypnotics, neuromuscular blocking agents, bronchodilators and anti-emetics) may be used effectively as a single dose, but drugs are most frequently given on a continuous basis. The following are examples of administration programs.

(i) Single intravenous injection.

(ii) Intravenous infusion at a constant rate.

(iii) A sequence of intravenous injections.

(iv) Single oral ingestion in tablet or liquid (solution) form

(v) A sequence of oral ingestions.

As we have seen the one-compartment model can be applied to case (i). It is not *a priori* obvious that this model can be applied to cases (ii) and (iii) but experiment has shown that it can in fact also be used to describe these cases. We proceed now to discuss the administration of drugs according to programs (ii) - (v).

Case (ii)

The model equations are:

$$\frac{dc}{dt} = r - kc \qquad (2)$$

$$c(0) = 0$$

where $r = R/V$ and R is the amount of drug infused per unit time. The assumption that V has the same value as in case (i) is verified by experiment [13]. The solution to (2) is

$$c(t) = \frac{r}{k}(1 - e^{-kt})$$

so that the concentration in plasma evolves towards a steady-state or *plateau* level, r/k. Thus it is possible to establish a fixed concentration of drug in plasma (and presumably in the rest of the body). The plateau-effect provides the basis for much of drug therapy. If a range of plasma levels can be identified for which the therapeutic effect is manifested (the *therapeutic range*) then the objective is to get the plasma level into this range and to hold it there for as long as is necessary. The upper limit is the concentration at which toxic effects appear and the lower limit is the minimum effective level. For drugs with large half-lives (e.g. quinacrine) an initial priming dose is essential in order to rap-

idly achieve the therapeutic effect. In this case

$$c(0) = D/V$$

and

$$c(t) = \frac{r}{k} - (\frac{r}{k} - c(0))e^{-kt}$$

where D is the amount of priming dose. In order to achieve a rapid effect D should be chosen close to R/k.

Case (iii)

Let the amount of each injection be A and let τ be the time interval between injections. At time $j\tau$, $j = 0, 1, 2, \ldots$, the plasma level will jump by an amount $a = A/V$. The model equations are

$$\frac{dc}{dt} = \sum_{j=1}^{n} a\delta(t - j\tau) - kc$$

$$c(0) = a$$

where δ is the Dirac delta-function. The problem may more easily be formulated as a sequence of initial-value problems. Let $c_n(t)$ denote the plasma-concentration between the (n-1)th and n th injections where t is now measured relative to the time of the (n-1)th injection. Then

$$\frac{dc_n}{dt} = -kc_n \ , \ 0 < t < \tau$$

$$c_n(0) = c_{n-1}(\tau) + a \ , \ n = 1,2,\ldots.$$

where $c_0(\tau)$ is defined to be zero. Then

$$c_n(t) = c_n(0)e^{-kt}.$$

The initial conditions may then be employed to recursively compute:

$$c_{n+1}(0) = ae^{-nk\tau} + a\frac{(1 - e^{-nk\tau})}{(1 - e^{-k\tau})},$$

$$c_\infty(0) = \lim_{n\to\infty} c_n(0) = \frac{a}{1 - e^{-k\tau}}$$

and

$$c_\infty(\tau) = \lim_{n\to\infty} c_n(\tau) = \frac{ae^{-k\tau}}{1 - e^{-k\tau}}$$

Hence, a 'plateau' is also established in this case, but now there are oscillations between fixed limits, as indicated in Figure 2.

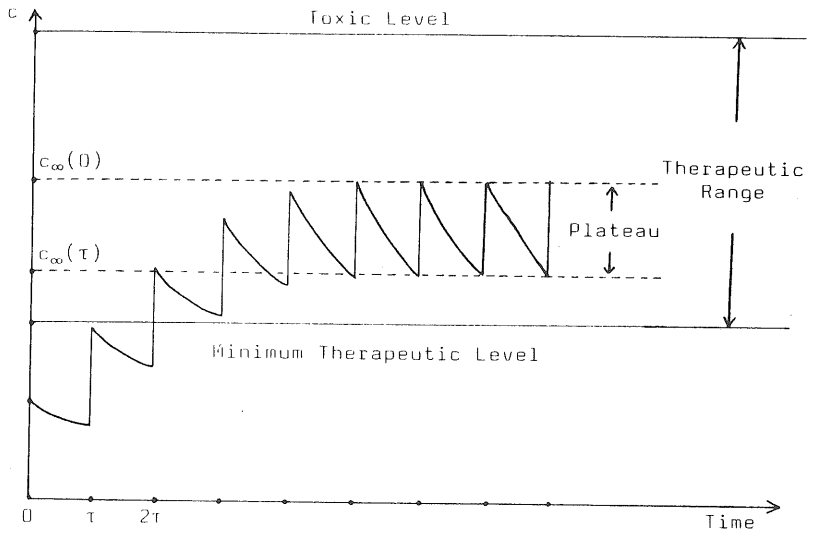

FIGURE 2

If a priming injection equal to $Vc_\infty(0)$ is given the plateau level will be immediately established.

Case (iv)

A tablet or capsule, which dissolves readily in the gastro-intestinal fluid, is the most common form of drug preparation for oral administration. If the plasma concentration of a drug falls in a mono-exponential fashion following intra-

venous injection it will exhibit a bi-exponential behaviour if administered orally [13,15]. The typical plasma concentration curve is indicated in Figure 3. The small intestine is the major site for drug (and nutrient) absorption due to its large surface area (about 200 m^2) and high vascularity [7].

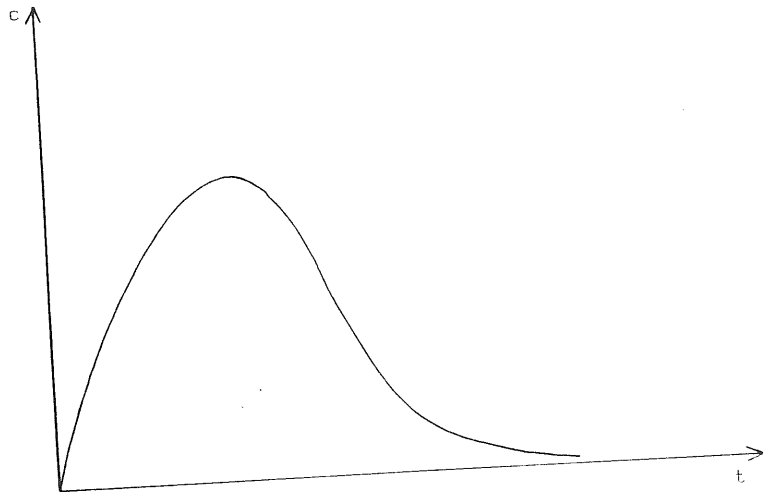

FIGURE 3

Drug which is transported from the intestinal fluid across the cells of the intestinal wall into the blood will be continuously removed by convection. The concentration of drug in blood returning to the intestine will be low (due to distribution) in comparison with that in the intestinal fluid. Hence a high concentration gradient will exist practically throughout the absorption process which implies that drug-transfer is a one-way process [16]. There is a further dimension to compartmental modelling which arises in the multi-compartment case. Identification of coefficients becomes a problem. This is partially circumvented by introducing

mass-balance principles. The models are formulated in terms of the total amount of drug in each compartment, rather than in terms of concentrations, and the assumption is made, as mentioned previously, that concentrations in various parts of a compartment are proportional to the total amount. In the current case, the gastro-intestinal tract may be viewed as one compartment and the remainder of the body as another. The model equations in this case are:

$$\frac{dG}{dt} = -\ell G$$

$$\frac{dC}{dt} = \ell G - kC \qquad (3)$$

$$G(0) = D$$

$$C(0) = 0$$

where G and C are the amounts of drug in the gastro-intestinal tract and the body, respectively, and D is the amount of the dose. The magnitudes and signs of the system matrix coefficients are chosen to conserve mass and to incorporate directions of mass transfer. Thus, the rate of loss of drug from the gastro-intestinal tract is equal to the rate of entry of drug into the body. Eqautions (3) are usually expressed in the form:

$$\frac{dC}{dt} = \ell De^{-\ell t} - kC \qquad (4)$$

and pharmacologists consider this to be a one-compartment model with time-dependent rate of administration. The solution is

$$C(t) = \frac{\ell D}{\ell - k}(e^{-kt} - e^{-\ell t}) \qquad (5)$$

and the plasma concentration is given by

$$c = C/V$$

where V can be found from an intravenous injection experiment. The duration of action of the dose (during which c exceeds the minimum therapeutic level) can be computed (using Newton's method for example) from equations (4) and (5).

Case (v)

The most common form of oral drug-administration program consists of a priming dose followed by a sequence of smaller maintenance doses. The problem is most easily formulated as a sequence of initial-value problems, as in case (iii). Let $C_n(t)$ and $G_n(t)$ denote the amounts of drug in the body and gastro-intestinal tract, respectively, during the interval $((n-1)\tau, n\tau)$. Let D and E denote the amounts of the priming and maintenance doses, respectively. The sequence of initial-value problems is:

$$\frac{dG_n}{dt} = -\ell G_n \quad , \quad 0 < t < \tau$$

$$\frac{dC_n}{dt} = \ell G_n - kC_n$$

$$G_n(0) = G_{n-1}(\tau) + E$$

$$C_n(0) = C_{n-1}(\tau)$$

$$G_1(0) = D$$

$$C_1(0) = 0$$

The expression for C_n is complicated and is best computed recursively on a computer. A plateau also occurs in this case and it is easily shown that:

$$C_\infty(t) = \lim_{n\to\infty} C_n(t) = \frac{\ell D}{\ell - k}\left\{\frac{e^{-kt}}{1 - e^{-k\tau}} - \frac{e^{-\ell t}}{1 - e^{-\ell\tau}}\right\}$$

which oscillates between the lower limit $C_\infty(0) = C_\infty(\tau)$ and the upper limit $C_\infty(\tau)$ where

$$\tau = \frac{1}{\ell - k}\ln\left\{\frac{\ell(1 - e^{-k\tau})}{k(1 - e^{-\ell\tau})}\right\}$$

The effect of the priming dose is transient and serves only to access the plateau level rapidly. An example, indicating the evolution of the drug level, is given in Figure 4.

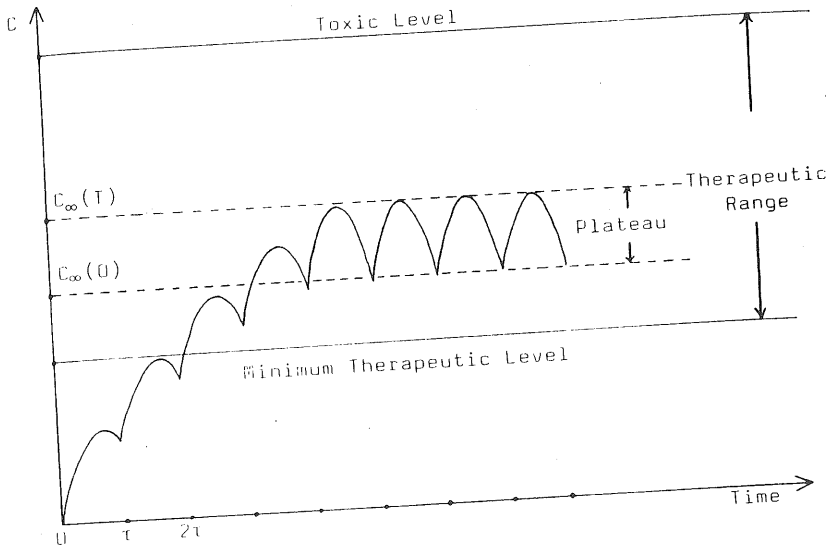

FIGURE 4

The design of the administration program is more complex in this case and requires the use of numerical methods. It is usually further complicated when time intervals between doses are not constant (e.g. during the night).

Multiple-Compartment Models

The one-compartment model is applicable to drugs that distribute very rapidly throughout the body. Many drugs, however, have a distributive phase that lasts for hours or even

days. For such drugs, plasma concentration curves (following intravenous injection) typically display a rapid initial decay [13] as indicated by the X-curve in Figure 5. All multi-compartment models are assumed to contain the blood in a single compartment (known as the *central* compartment). All other compartments are termed *peripheral*. The question of the nature of elimination of drug is important in the construction of model equations. In most cases it is reasonable to assume that elimination takes place from the central compartment alone since it is likely that the highly vascular liver and kidney are contained therein. Other elimination pathways are usually negligible [15]. The equations for the two-compartment model are therefore given by (in the case of intravenous injection):

$$\frac{dX}{dt} = k_1 Y - k_2 X - k_0 X$$

$$\frac{dY}{dt} = -k_1 Y + k_2 X$$

$$X(0) = D$$

$$Y(0) = 0$$

where X and Y denote the *amounts* of drug in the central and peripheral compartments, respectively. The term involving k_0 represents elimination from the central compartment and the magnitudes and signs of the system matrix are based on mass-balance principles. The link with reality is again obtained by postulating that the blood-plasma concentration, c, is proportional to X:

$$c = X/V$$

Data analysis will yield

$$c = Ae^{-\alpha t} + Be^{-\beta t}$$

It is then possible to solve (uniquely) for the coefficients k_0, k_1, k_2 and V in terms of A, B, α and β [13]. This would

not be possible if the system matrix was assumed to be a general 2x2 matrix. The value of V obtained in experiments is usually greater than 3 litres which again indicates an early rapid transfer of drug out of plasma into the remainder of the central compartment [13]. Typical curves for X and Y are shown in Figure 5.

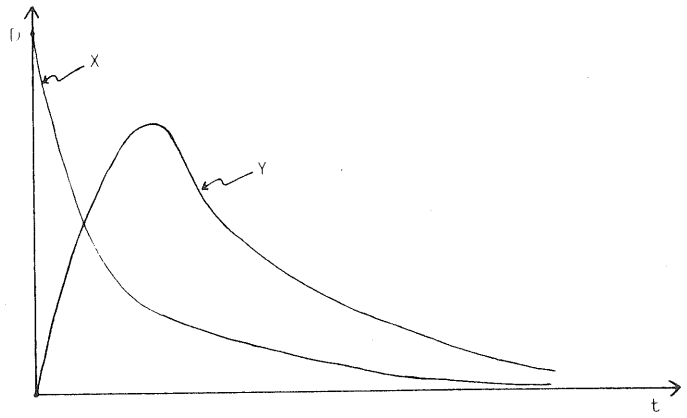

FIGURE 5

If $\alpha >> \beta$ the amount of drug in the peripheral compartment will peak early and the subsequent decay in both compartments will rapidly become mono-exponential. Since the number of compartments is unknown, *a priori*, it is important to sample plasma levels frequently in the early stage. The single intravenous injection data may be used to design infusion and multiple-injection programs, as in the one-compartment case. Similar considerations apply to oral-dosing programs.

Three-compartment models have been developed for a number of important drugs (e.g. thiopental - a short-acting and widely-used anaesthetic [17] and d-tubocurarine - a neuromuscular blocking agent [18]). There are many possible models that could produce tri-exponential behaviour. It is usually

assumed that no direct drug transfer occurs between the peripheral compartments in addition to the central elimination assumption [13].

If the drug receptors were in a peripheral compartment the relationship between plasma-level and effect would be less than obvious. If it were true that drug concentrations at various sites in a peripheral compartment were proportional to the amount of drug in that compartment it would be possible to relate the pharmacologic effect to the peripheral compartment drug level. Such a relationship was found for the hallucinogenic drug lysergic acid diethylamide (LSD) in a study on five human subjects but further studies are probably warranted to establish the model [18]. It is also known that brain levels of the anaesthetic γ-hydroxybutyric acid in rats are the same when animals fall asleep and when they awaken while the corresponding plasma levels are quite different [19]. However, the author is unaware of any study of this drug that would substantiate a multi-compartment model.

It is possible that therapeutic and toxic effects could occur in different compartments. Such a situation could give rise to interesting constrained optimization problems in the design of administration programs where the objective would be to maximise the therapeutic effect while minimizing, in some appropriate clinical sense, the toxic effects [20].

Non-Linear Models and Problems

The biotransformation and renal tubular secretion pathways of drug elimination are mediated by enzymes (usually proteins). The simplest drug-enzyme reaction is that in which drug and enzyme molecules react to produce a drug-enzyme complex which then dissociates to produce a metabolite (inactive) and the original enzyme. The enzyme concentration is usually very small in comparison with that of drugs. The same enzyme molecules react repeatedly with the drug molecules to gradually

lower the concentration of drug. The reaction is governed by a system of two first-order non-linear differential equations, which can be approximated using a singular-perturbation procedure to yield the single equation:

$$\frac{dc}{dt} = \frac{-Vc}{K + c} \qquad (6)$$

for the drug concentration, c, where V and K are constants [6,21]. The solution of (6) is a uniform asymptotic expansion of the true solution with error or order E/D, where E and D are the initial enzyme and drug concentrations respectively. Equation (6) would be valid *in vitro* but it could hardly be expected to model the evolution of plasma concentration *in vivo* (in the case in which biotransformation is the main elimination pathway). However a number of drugs have plasma decay curves which agree qualitatively with the solution of (6). If $c >> K$ the decay rate is approximately constant (the process is said to *saturate*) and if $c << K$ the decay is approximately exponential. The latter result suggests that drugs, which behave in accordance with the earlier one-compartment model and are eliminated by biotransformation, are present in concentrations well below the saturation level. The major anti-epileptic drug, phenytoin, conforms to model (6) [22,23]. Other examples are ethanol (alcohol) [24] and aspirin [7]. In the case of alcohol, $c >> K$, in the 'therapeutic' range. The therapeutic range for phenytoin is quite narrow (10 - 20 micrograms/millilitre). The minimum desired effect is elimination of epileptic seizures. Toxic effects include ataxia and psychological disturbances. Further the fully-nonlinear behaviour occurs in the therapeutic range. There is a further effect which makes clinical treatment difficult. The drug is usually given orally (one tablet per day) for chronic treatment. Consider, for simplicity, the case of continuous intravenous infusion for which the equations are:

$$\frac{dc}{dt} = r - \frac{Vc}{K + c} \quad , \quad t > 0$$

$$c(0) = 0$$

It may easily be shown that c increases up to the plateau level

$$c = \frac{rK}{V - r}$$

if $r < V$, but that the concentration increases without bound if $r > V$. Thus, the plateau is unstable if r is close to V. This is usually the case in practice. Similar considerations apply in the case of multiple oral-dosing. Further, the design of administration programs for this drug requires numerical integration techniques. Adjustments of dosage would also require care and this model is very useful in such a situation [18,22].

A phenomenon, known by the misleading name of *protein binding*, is considered to be of paramount importance in Pharmacology [15]. All drugs undergo *reversible* chemical reactions with proteins (mainly albumin) in the blood. Proteins and drug-protein complexes cannot diffuse through the cells of arterial and venous walls. Hence, protein binding will influence the distribution of drug. The ratio of the concentration of total drug and that of drug-protein complex appears to be constant over the therapeutic range for the majority of drugs under most conditions. A number of drugs (e.g. phenylbutazone - a powerful anti-inflammatory agent, clofibrate - an inhibitor of cholesterol synthesis, naproxen - used to treat gout) exhibit non-linear effects, in the therapeutic range, which are believed to be attributable to protein-binding. Reduced plasma levels of proteins (which occur in some diseased states and in the newborn) may also cause such effects to be manifested. The subject is surrounded by controversy in the pharmacological literature. Both compartmental [25,26] and physiological [27] models have been considered. Part of the contr-

oversy concerns the effect of protein-binding on elimination and the physiological models deal only with liver or renal function and have not been incorporated into whole-body models. The governing differential equations are non-linear in both cases and have been solved using numerical integration routines. The simplest models contain at least five parameters which makes it difficult to extract a qualitative picture from numerical solutions. The author has recently carried out a singular-perturbation analysis of some of these models which identifies conditions under which the phenomenon may have importance [28]. There seems to be no consensus yet on the status of the various models.

A related, but more complex, problem is that of *drug-interactions*. It is frequently necessary to administer a number of drugs simultaneously. Unfortunately, most drugs interact in a non-linear fashion when co-administered. A number of possible mechanisms of interactive behaviour are understood but are unquantified [7,15]. Mathematical modelling in this area appears to be non-existent.

Some drugs exert their effects, not on the human being directly, but on an invading population of bacteria (which can cause many serious diseases such as tuberculosis and bubonic plague). Compartmental models have been developed for most antibiotics but a satisfactory understanding of the relationship between the nature of the administration program and effect may require incorporation of bacterial population dynamics [14]. An iatrogenic phenomenon known as *superinfection* may occur if a drug disturbs the population balance of micro-organisms in the body. Such a disturbance may allow a species to grow to a size at which it becomes pathogenic. Penicillin, for example, is fatal in guinea pigs for this reason [29]. Mathematical modelling appears not to have been attempted in this area.

Conclusion

Mathematical modelling has contributed significantly to the understanding of many drugs and to rational and safe drug therapy. The subject is recognized as being of increasing importance in Clinical Pharmacology. There are now two medical journals on the subject [30,31]. A need for more physiological modelling has been expressed in recent reviews in Clinical Pharmacology [32,33] which indicates a perception that more advanced mathematical modelling is required for continued progress. There would thus seem to be considerable scope for collaboration between mathematicians and pharmacologists in this area.

The value of statistics has long been appreciated in medical education. A lot of insight can be gained in Pharmacokinetics with a modest background in calculus and differential equations. When one considers the extent of drug therapy in the treatment of disease there seems to be a strong case for the inclusion of mathematical modelling in the medical curriculum.

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