'MacDOPE': A SIMULATION OF DRUG DISPOSITION IN THE HUMAN BODY: APPLICATIONS IN CLINICAL PHARMACOKINETICS

RALPH BLOCH, GEORGE SWEENEY & KHURSHEED AHMED

McMaster University, Faculty of Health Sciences,
Hamilton, Ontario, Canada L8N 3Z5

C. JOHN DICKINSON & DAVID INGRAM

St. Bartholomew's Hospital Medical College,
Department of Medicine,
London EC1A 7BE, England

1 We have described a novel approach to absorption, distribution, metabolism and elimination of drugs in which the patient is described using 23 Patient Factors and drugs by up to 50 Drug Factors. Kinetic behaviour of a drug results from the interaction of patient and drug factors according to equations describing an eight compartment model. In this model non-linear processes (protein binding, hepatic drug metabolism and renal tubular transport) are handled by derivations of the law of mass action which have been generalised to permit the consequences of multiple drugs interacting at single macromolecular sites to be correctly calculated.

2 The mathematical description of this model is provided in a companion paper and solution of the equations is only possible using a digital computer. The computer programme is provided with an interactional format which makes operation independent of mathematical skills. Patients are defined by age, sex, height and weight with, or without, organ dysfunction; the programme then generates appropriate factors. Drug enters the system when a prescription is typed on the keyboard and required Drug Factors are then retrieved from the disc files. Drug concentrations in plasma or body fluids are given as simple graphs as a function of time, or in tabular form.

3 Any of the Patient or Drug Factors may be altered before, or during a run and up to three drugs may be simulated at one time thus permitting certain kinetic interactions to be examined. The scope of the simulator is illustrated using aspirin: pH dependent gastric absorption, first-order conversion of aspirin to salicylate, partly first order and partly saturable hepatic metabolism of salicylate, and the complex renal handling of this drug are all represented. Interaction of phenytoin with salicylate has been examined quantitatively to suggest limited clinical relevance for the observed displacement of phenytoin from serum albumin. The use of the simulator in a short course of pharmacokinetics is briefly described.

Introduction

Pharmacology, the study of the actions and uses of drugs, embraces two major areas: pharmacodynamics is concerned with the effects of drugs at receptors, whether real or hypothetical, while pharmacokinetics is concerned with the determinants of drug concentration as a function of time at such receptors. Much empiric drug data has been collected describing concentrations of drugs present in biological fluids at different times after administration by various routes. Pharmacokinetics is concerned with theoretical approaches which describe and predict data of this type.

If drug absorption, distribution and elimination can be described as the sum of first order processes where net movement of drug between different regions is proportional only to time and differences in drug

concentration, plasma levels of drug can then be simulated by representing the body as two (or more) compartments. Drug concentrations at time, t , for a two-compartment model are described by the linear differential equation:

$$C_t = A_0 e^{-\alpha t} + B_0 e^{-\beta t} \dots (1)$$

Where: C = Drug concentration
 t = Time elapsed after drug administration

A_0 } zero-time drug concentrations
 B_0 } = chosen to fit the particular system analysed

α } = rate constants for a bi-exponential process
 β }

This approach has been widely used in the clinical literature (Greenblatt & Koch-Weser, 1975). Additional compartments can be added with a corresponding increase in the complexity of the equation.

Unfortunately, when equation (1) is fitted to data on drug concentration in plasma as a function of time, the co-efficients A , B , α and β obtained correlate only to a limited extent with known physiological mechanisms. Also, A , B , α and β result from the interaction of properties of a specific drug and a specific patient so that solution of equation (1) for one drug does not necessarily permit extrapolation to other drugs and/or patients. An attractive feature of this type of model has been its mathematical simplicity. However, even this has been sufficiently daunting that it is seldom consciously used to assist in designing therapeutic regimens except by health professionals with a special interest in pharmacokinetics.

An alternative approach to the prediction of drug levels as a function of time would be to define those properties of a drug which determine its interaction with a biological system, and to allow the drug to interact with an organism for which physiological and biochemical determinants of drug disposition have also been defined. For the drug, properties such as fat solubility, pK and molecular weight would need to be specified. To define the organism, volumes of the main identifiable compartments separated by permeability barriers, the nature of these barriers, the amount of lipid, the binding characteristics of macromolecules, metabolic pathways and regional differences in pH would be necessary information. Consideration should also be given to the role of circulation in distributing drugs. Such a model of drug distribution could be termed 'physiological'; it would necessarily be complex and it would call for a considerable amount of information not readily available. Nevertheless, several models possessing some of these features have been described (Bischoff, Dedrick, Zaharko & Longstreth, 1971; Harrison & Gibaldi, 1977; Luecke & Wosilait, 1978) in order to improve upon more standard pharmacokinetic approaches to drugs such as digoxin and methotrexate.

The purpose of this paper is to present a more general pharmacokinetic simulator which can represent the distribution of a wide range of drugs in both healthy and ill persons and generate data reflecting drug concentration as a function of time in various biological fluids. As the model to be presented considers drug-protein interactions (including enzymes), non-linear kinetics consequent on protein binding or saturation of metabolic pathways are taken into account. The equations have been written to consider up to three drugs simultaneously present so that drug interactions due to competition for protein binding sites or inhibition of drug metabolising enzymes are also considered. However, the model to be described

ignores pharmacodynamic effects and does not simulate changes in drug disposition attributable to alterations in circulatory beds in a rigorously defensible fashion.

The resulting mathematical formulation is complex and forms the subject matter of a companion paper (Bloch, Ingram, Sweeney, Ahmed & Dickinson, 1980). Solution of the equations is possible only by digital computer. However, the interactive format provided with the program makes it readily accessible to health professionals without mathematical skills. The simulator has been developed for both research and educational purposes; both uses will be described in this paper. This is the fourth in a series of interactive computer simulations developed jointly at our institutions (Dickinson & Shephard, 1972; Dickinson, Goldsmith & Sackett, 1973; Dickinson, 1977) and for quick reference is called *MacDope*.

Description of MacDope

Figure 1 provides a graphic discription of the model. The user who calls up this program from an interactive terminal is first given the option of a brief description and is then asked to define a patient. This may be done by supplying the age, height, weight and sex or by choosing 'preset' patients such as 'a healthy adult male volunteer', 'a three-year old girl' or 'a sixty-year old woman in renal failure'. A algorithm based on published data (Schock, 1966; Fomon, 1967; Edelmann & Spitzer, 1975) then assigns appropriate values for the major body fluid spaces illustrated in Figure 1 (plasma, extracellular and intracellular), for lean body mass and for body fat. Glomerular filtration rate, renal tubular and hepatic function are weighted in proportion to the lean body weight and related to function in a healthy 70 kg adult male or modified appropriately to simulate disease states. The complete set of patient factors for such an individual is provided as Appendix B.

After specifying a patient the user is asked to enter prescriptions. Currently about twenty drugs are available on the files and prescriptions, comprising drug name, dose, route and timing for up to three different drugs, may be entered serially. Oral, intramuscular subcutaneous and intravenous routes, or a continuous IV infusion are permitted. A drug will enter the system immediately if the time of administration is specified as 'stat', or abbreviations such as 'Q6H' and 'TID' may be used to designate multiple dose regimes.

When the patient has been chosen and the drug (or drugs) prescribed the operator is given a number of choices. 'Change' is the most important because it permits the operator to alter, among other things, the patient (e.g. to simulate renal or hepatic disease) or the drug (e.g. to make it more or less lipid soluble). Any of the patients or drug factors listed in the

appendices may be changed even though changes may not necessarily be sensible. When desired changes (if any) have been made, the operator selects the option 'continue' and the program computes drug disposition according to the model illustrated in Figure 1. Results are available in various forms, either graphical or tabular, with operator control over plotting intervals and the duration of time for which drug disposition is to be simulated. For inexperienced operators standard conditions for the type and duration of the display are provided automatically.

Having provided the foregoing general account of the operation of MacDope it is necessary to consider problems which arose at various points in the simulation and the solutions that have been adopted. Readers interested in mathematical details are referred to the companion paper (Bloch *et al.*, 1980).

Choice of compartments

The choice of compartments represents a compromise. Plasma, interstitial and intravascular spaces were obviously required. Separate specification of a lipid compartment was desirable to accommodate fat soluble drugs and the user would need to adjust the size of this space appropriately as well as its rate-constant for equilibration with plasma. A separate small 'parenteral' space was required to act as a depot for injected drug. Simulation of absorption of drug taken by mouth required both gastric and intestinal compartments (at different pHs) and these come to equilibrium with a separate portal space in which metabolism occurs (see 'hepatic drug metabolism'). The portal space, in turn, equilibrates with plasma.

A brain, or cerebrospinal fluid space, has not been specified although this may be added in future. Although there is justification in available data for both 'fast' and 'slow' plasma spaces, only a single plasma compartment has been provided. The user may use one of the existing spaces to provide an additional slow component if simulation of drug distribution to poorly perfused tissues is of particular interest.

Intestinal 'drug absorption'

Tablet dissolution rate is an important determinant of drug absorption and the formation of soluble from solid phase drug is represented in MacDope as a zero order process. A rate constant determines the fractional transfer of gastric contents to the intestinal space with solid phase and dissolved drug being transferred separately using the same rate constant while the zero order process dictates the dissolution of solid drug present in both stomach and intestine. Drug not absorbed from the intestine is effectively lost from the system. However, to take some account of the temporal element of drug transit through the intestine, gut loss is subject to a delay arbitrarily set equal to the reciprocal of the rate constant for intestinal motility (factor 16 in Appendix B).

Protein binding in the plasma space

It should be pointed out that solution of the equations used to calculate plasma levels of drug in MacDope is not continuous but is performed in discrete steps representing intervals of time (the iteration interval) so adjusted that successive levels of free drug in the

Figure 1 Functional elements in the MacDope simulation are shown with the eight compartments numbered. Both glomerular filtration and tubular function are represented in the simulated kidney; these act on the drug concentration in the plasma compartment. Various routes for drug to enter the system are also shown. (P.O. = per os; I.V. = intravenous, and the 'parenteral' compartment can be used to simulate intramuscular or subcutaneous routes.)

plasma compartment do not change by more than 10% or less at the operator's discretion. During each iteration the distribution of drug in the plasma space between bound and free forms is first calculated according to a modified form of the equation (Goldstein, Aronow & Kalman, 1974.)

$$\beta = \frac{1}{1 + \frac{K_D}{nP} + \frac{(x)}{nP}} \quad (2)$$

where β is the fraction of drug bound, K_D is the dissociation constant from the Law of Mass Action, n is the number of binding sites on a protein molecule, (x) the concentration of unbound drug, and P the molar concentration of protein.

For reasons of computational convenience this equation has been used in the model in a rearranged form. K_A , an association constant is used in place of K_D , and the equation gives β as the ratio of free to total drug. This equation has also been generalized to permit competition among multiple drugs to be represented. One of the drug factors (38, Appendix B) specifies the drug-binding system, for example, anion-binding sites on albumin. Any two drugs must have the same value for this system factor for an interaction to be considered. Other factors required are the binding capacity of the specified class of site (Drug Factor 10, nmol/g) and the affinity constant, K_A (Drug Factor 11, nmol/l). Protein concentrations are, of course, 'patient factors'; albumin, for example, is Patient Factor 3 in Appendix B. In the **Results** section, an example will be given of the use of this aspect of the program to investigate the quantitative significance of displacement of phenytoin from binding sites on albumin by a second drug (salicylate).

Hepatic drug metabolism

The program has been designed so that simulated liver function operates on drug available in a space interposed between gut and plasma and in equilibrium with stomach, intestine and plasma. This space is regarded as containing plasma proteins so that the simulated hepatic processes operate on total, not free, drug. Drug within the hepatic space may be the substrate for a saturable and/or a first order process. Flux through these systems can be treated as a metabolite which then appears as a new drug in the system, or as unchanged drug; it may be lost from the system, or dumped immediately in the plasma space. Finally, unchanged drug or metabolite may be routed via a delay (currently set at 90 min) to the intestinal space from which reabsorption can occur. Appropriate choice of these options thus permits simulation of enterohepatic circulation of unchanged drug or a

metabolite via a saturable or first order transport process. 'First pass' drug metabolism by the liver may be simulated either by permitting only a preset fraction of absorbed drug to enter the hepatic compartment (Drug Factor, 8, Appendix A) or setting up hepatic drug metabolism to reflect correctly available empirical data. The second approach is preferred, but is a recent program development.

The potentially saturable kinetics of metabolic pathways are handled according to Michaelis-Menten kinetics. The equations used have been modified to accommodate more than one substrate competing for a single enzyme and expanded to give zero order and first order components which provide linear expressions within the limited periods of time represented by each iteration. As for the calculation of protein binding, a capacity factor, an affinity factor and a system factor are required. If two drugs are assigned the same system factor, competition for this single metabolic (or excretory) pathway will be taken into account during computation.

Handling of drug by the kidney

Patient factors which determine renal function include glomerular filtration rate (GFR), tubular function (1.0 for 70 kg male volunteer and adjusted in proportion to lean body mass), urine flow rate and urine pH. The product of GFR and free plasma drug concentration yields the filtered load which, divided by urine flow, gives the concentration of drug in the urine if no secretion or reabsorption takes place. It has been assumed that ionized drug will not tend to equilibrate between urine and plasma but that non-ionized drug may. This pH-dependent process is governed by a rate constant (Drug Factor 9: 'tubular permeability factor') which operates to reduce the difference in concentration of non-ionized drug between urine and blood as a first order process. The simulation of kidney function is completed by the provision of tubular reabsorptive and secretory processes which obey Michaelis-Menten kinetics, are handled mathematically as described for hepatic metabolism and similarly use generalized equations which permit more than one drug to be handled in order that interactions may be correctly represented when available empirical data indicates that these do, or might, occur.

Solution algorithm

The mathematical formulation of MacDope embracing equilibria between eight compartments defined as first order processes and the saturable processes involved in protein binding, in hepatic metabolism and renal tubular function, is clearly complex. The system has been represented as an electrical network; the first order components of saturable pro-

cesses can then be lumped with other first order terms operating between the same compartments. Capacitances of the compartments (in litres) are given as patient factors and conductance terms are then implicit in the specified rate constants. The system is driven by a series of negative or positive generators representing the zero order components. Within discrete domains of time (the iteration interval) the concentrations of free drug are solved for each point in the network using the standard Runge-Kutta subroutine. Again, further mathematical details are available in the companion paper.

Results

Operation of the MacDope pharmacokinetic simulator will be demonstrated with three applications. Firstly, essential features of the kinetics of aspirin will be simulated. This drug has been chosen because the wealth of data available from clinical emphasizes the complexity of its disposition in man and severely taxes a simulation. Secondly, the ability of the program to deal quantitatively with drug interactions by competition of two drugs for a single macromolecular site will be demonstrated. The displacement of phenytoin from binding sites on serum albumin by a second drug (salicylate) serves as an example. Thirdly, use of this program in a short course on pharmacokinetics will be described.

The handling of acetylsalicylic acid

It was considered that the simulated handling of aspirin should demonstrate the following features: (a) acetylsalicylic acid should be converted to salicylate with a half-life of approximately 20 min (Woodbury & Fingl, 1975); (b) the volume of distribution of salicylate should be realistic; Cumming, Dukes & Widdowson (1964) found 0.22 ± 0.03 l/kg in 4 normal subjects; (c) gastric absorption (of aspirin) should be pH dependent although the greater part of gastro-intestinal absorption should be intestinal (Woodbury & Fingl, 1975); (d) clearance of salicylate from plasma should be via both hepatic and renal mechanisms; (e) hepatic clearance should demonstrate a first order component with a rate constant of 0.017 h^{-1} and a saturable component with a maximal velocity of about $1.3 \text{ mg kg}^{-1} \text{ h}^{-1}$. (Actually, this combines separate saturable pathways leading to salicylurate and salicylphenolic glucuronide with average Michaelis constants of 32.2 mg l^{-1} and 60 mg l^{-1} respectively; for the purposes of simulation of single K_m of 50 mg l^{-1} has been chosen) (Levy & Tsuchiya, 1972); (f) renal clearance of salicylate should be by glomerular filtration of the unbound fraction as well as by tubular secretion. When the urine pH reached 7.8 the clearance of salicylate was shown by Morgan & Polak

(1971), to exceed the glomerular filtration rate. As salicylate is known to be from 50–70% protein bound this suggests that tubular secretion is occurring. The same authors demonstrated a roughly linear relationship between the logarithm of salicylate clearance and urine pH; thus: $\log \text{Cl}_{\text{SAL}} = 0.67 (\text{pH}_{\text{urine}} - 3.21) + C$, where C is a constant of proportionality.

The conversion of aspirin to salicylate is simulated as the first order conversion of drug in the plasma compartment and drug factor 25 specifies the rate constant for this process. Drug Factor 37 specifies the code number of the drug formed (in this case salicylate) and Drug Factor 35 selects between disappearance of drug, return to the plasma (in this case) or re-entry of the intestine via the enterohepatic delay. Volume of distribution is given by the following expression:

$$V_{\text{Dist}} = P_4 + P_{20} + (1 - \text{PB}\%) \left[\frac{(P_5 \times D_3) + (P_6 \times D_{15})}{100 + (P_7 + D_5 \times D_{15})} \right]$$

where 'P' signifies a patient factor (4 = plasma space, 5 = lipid space, 6 = interstitial space, 7 = intracellular space and 20 = portal space) and 'D' a drug factor (3 = lipid/water partition, 5 = intracellular to interstitial ratio, and 15 = interstitial to plasma drug concentration ratio). PB% refers to the percentage of drug protein bound in the plasma space. As protein binding varies with plasma salicylate concentration, volume of distribution, defined as the quantity of drug in the system divided by the plasma concentration, is dependent upon the dose of drug used in the determination. In a simulation such as this, determination of the volume of distribution is simplified by setting hepatic and renal function to zero and allowing the system to come to equilibrium. The drug and patient factors given in the appendices result in a volume of distribution for salicylate of 0.2 l/kg after a single 300 mg dose, but over 0.3 l/kg after a simulated overdose. Protein binding was 70% and 45% at plasma salicylate concentrations of 100 mg/l and 500 mg/l respectively.

Figure 2a demonstrates the rate of appearance of salicylate (trace B) in plasma after a single oral dose of 500 mg aspirin (plasma aspirin in curve A). Hepatic and renal function were set to zero and 1 g of salicylate was given orally (liquid formation) to generate Figure 2b. Trace A was generated with gastric and intestinal absorption functioning normally. Traces B–E represent gastric absorption alone at gastric pH values of 1.5, 2.5, 3.5 and 4.5 respectively, in order to demonstrate the marked pH dependence of gastric absorption in this simulation. Intestinal absorption is, of course, also pH dependent but with the intestinal pH set at 7.5, a large rate constant for intestinal absorption serves to represent the proportionally large surface area available for absorption.

Figure 2 (a) illustrates the conversion of an oral dose of aspirin (trace A) to salicylate (trace B) during a simulation in which salicylate metabolism has been set to zero. In (b), (A) illustrates absorption of aspirin with conversion to salicylate set to zero. To generate traces (B)–(E), intestinal absorption has also been set to zero leaving only the gastric component. In (B), gastric pH is 1.5 but this has been raised to 2.5 (C), 3.5 (D) and 4.5 (E) to demonstrate the simulation of this pH dependent process.

Figures 2c and d deal with simulations of elimination. In 2c, trace (A) simulates the clearance of salicylate by the first order process alone. When the saturable hepatic pathways (see text) are added, trace (D) results. Renal function was inoperative for these two simulations. When renal function was restored and hepatic function set to zero, trace (B) was obtained for glomerula filtration rate (GFR) alone and trace (C) for GFR combined with tubular function with the simulated urine pH at 5.5. When the separate renal and hepatic clearances of traces (C) and (D) were combined, (E) resulted, and when urine pH was raised from 5.5 in (E) to 7.5 trace (F) was obtained for salicylate clearance by hepatic and renal processes at a urine pH of 7.5.

Figure 2d shows the simulated treatment of salicylate intoxication in a normal volunteer. Without treatment clearance followed trace (A); when a diuresis of 0.3 l/h was instituted trace (B) resulted and if this regime was combined with alkalinisation of the urine a further increase in clearance was obtained as shown in trace (C).

Figure 2c demonstrates the dissection of salicylate elimination. Trace A simulates elimination due only to first order hepatic processes while trace D shows this combined with the saturable hepatic pathways. Trace B shows elimination due to glomerular filtration alone and trace C that due to GFR and tubular secretion; both B and C represent clearance when the urine pH is 5.5. Trace E combines both hepatic and renal processes without any change in the urine pH but in curve F using pH has been raised to 7.5. In the final part of this figure (2d), trace A shows simulated salicylate intoxication without treatment (and, of course, the simulated volunteer remains normal). In trace B a diuresis of 0.3 l/h has been simulated and in curve C the urine pH has also been increased from its 'normal' value of 5.5, to 7.5. Two factors contribute to non-linearities in the semilogarithmic plots of elimination in Figure 2; as already pointed out, the volume of distribution decreases as plasma salicylate levels decrease due to changed levels of protein binding, and small non-linearities are due to plasma drug levels reaching and exceeding the association constants for the saturable hepatic enzyme systems.

Figure 3 A computer simulation of the following events is shown. Hepatic and renal function of a healthy volunteer were set to zero and equilibration with 630 mg phenytoin allowed to occur prior to zero time. These functions were then restored, and after a 2 h period of observation 1 g of salicylate was administered intravenously as a bolus. The binding of phenytoin to serum albumin was perturbed with displacement of bound drug from plasma into other body fluids. As salicylate levels in the plasma declined, slow and partial reversal of this perturbation occurred.

A simulated interaction between phenytoin and salicylate

A simulation was run to consider the possible quantitative significance of an interaction between the anti-convulsant drug phenytoin, and salicylate. The simulated disposition of salicylate has already been discussed. Phenytoin disposition was modelled using a single saturable metabolic pathway with a K_m of 15 mg/l and V_{max} of 40 mg/h which provides appropriate non-linear kinetics (Arnold & Gerber, 1970). Binding to serum albumin was set up with an affinity constant to give 90% binding at 15 mg/l which is an average therapeutic level (Lunde, Rane, Yaffe, Lund & Sjöqvist, 1970). The volume of distribution assigned to the drug in the model is 0.6 l/kg (Gugler, Manion & Azarnoff, 1976) which, in view of the extensive plasma protein binding, required concentration of the drug in either fat, cells, or both.

A simulated normal healthy male volunteer was given 630 mg phenytoin and, with hepatic and renal function set to zero, allowed to equilibrate for 12 h. Then, (time = 0 on Figure 3) excretory functions were restored and, after a 2 h delay, 1 g of salicylate was given i.v. Both free and total drug levels have been plotted. It is evident that in this simulation the dose of analgesic drug chosen was sufficient to cause a redistribution of phenytoin between the plasma and other body compartments, but that the increase in plasma free drug level was short-lived and would not be expected to have clinical significance.

Use of MacDope in a pharmacokinetics course

Forty-two fourth-year students were enrolled in a course entitled 'Molecular Pharmacology' as part of their Honours Biochemistry degree requirement. A portion of this course provided instruction in drug disposition and this was organized around the MacDope simulation. Lectures were followed by an assignment with unlimited access to the interactive computer program via video terminals with a hard copy option. The ten 40-min lectures dealt with drug absorption, distribution, metabolism and elimination; for each process the role of relevant patient and drug factors (Appendices A and B) was discussed. Comparisons were made between the two compartment open models and MacDope simulations so that interpretations of published data based upon the former model would be intelligible. Students were then required to choose any drug not already in MacDope files (there were twenty), to search published material for experimental data describing the disposition of the drug chosen in man, and to provide the drug factors necessary to simulate this data using the computer. Poorer students tended to use 'trial-and-error' approaches which were costly of computer time and inefficient in the selection of those factors it

was most critical to program correctly. Good students mastered the available literature and extracted descriptions of pharmacokinetic behaviour expressed in terms of volume of distribution, rate constant of elimination, with, or without, information on drug absorption with analysis according to one or two compartment models. The better students succeeded in basing satisfactory choices of MacDope factors on the data in order to create simulations consistent with published data. It was concluded that successful students in this course had used the computer-based simulation to link pharmacokinetic behaviour described according to more abstract models with the physiological and biochemical principles which, in fact, determine this. Drugs simulated included methotrexate, prednisone, probenecid, paracetamol, morphine, diazepam and ampicillin. Although the mathematical abilities of the class were variable, there was no complaint that this was a limitation in completing the assignment.

Discussion

We have described a novel approach to pharmacokinetics. Conventionally, analytical methods use equations which describe concentrations of a single drug as a function of time, assuming the body to comprise one or two anatomically undefined spaces. Instead, we have assumed the usual physiological divisions of the body fluid spaces and written equations to describe the movement of drugs between these. In addition, we have provided equations which describe various drug-macromolecule interactions and expanded these to deal with more than one drug. The result is a generalized pharmacokinetic simulator which, given an extensive array of data about a drug, will calculate levels in body fluids, indicate the effects of organ dysfunctions and predict the quantitative significance of kinetic drug interactions.

It is evident when Appendix B entitled 'drug factors' is scanned that the program requires information about drugs that is not readily available. Some of this has to be obtained by running the program to generate some of the drug factors. However, these factors, which include tubular maximum and various association constants, are physiologically meaningful and make explicit the physiological and biochemical determinants of pharmacokinetic behaviour.

A second limitation is associated with use of concentration of drug in computation rather than quantity of drug. As discussed in the companion mathematical paper, it is simpler to set up equations to follow this approach. However, this prevents realistic representation of circulatory factors in the model as it currently stands. This could cause inaccuracy in the adequate simulation of drugs cleared rapidly by the liver where circulatory function is all important.

The simulated handling of aspirin was quite involved despite the wealth of published data on the kinetics of this drug. Except for the view that the bulk of absorption is intestinal, we had no precise guidance in assigning relative importance to the highly pH-dependent gastric absorption (Figure 2b). Conversion to salicylate by a first order process (Figure 2a) was straightforward although it is worth noting the slow exponential components imposed on this process as aspirin diffuses back to the plasma space from deep spaces entered while plasma levels were high. The elimination of aspirin is of more interest. Saturable and non-saturable hepatic processes, glomerular filtration of unbound salicylate, tubular secretion of salicylate and reabsorption of the non-ionised component in the tubules have all been separately represented. Again, this was based on published data. The work of Levy and his associates (Levy & Tsuchiya, 1972; Levy, Tsuchiya & Asmal, 1972), the regression equation for pH dependence (Morgan & Polak, 1971) and the knowledge that salicylate is protein bound, making it impossible for clearance to equal glomerular filtration rate without a tubular secretory component, were all taken into account (Figure 2c). This made possible a comparison of different approaches to the treatment of salicylate poisoning with results consistent with those observed clinically (Cumming *et al.*, 1964).

The possible importance of displacement from sites of protein binding of one drug by a second drug has often been referred to and it was of interest to use the model to evaluate this quantitatively. The point to stress, and shown in Figure 3, is that the disturbance in the example chosen is transient. Free plasma phenytoin does increase by about 50% following an intravenous bolus of salicylate, but displaced drug rapidly equilibrates with the remaining pool of drug in the body to re-establish a plasma level of free phenytoin quite similar to that prior to the interaction. A possible fallacy is that the model does not assign sufficient albumin to the interstitial space, but data to evaluate the importance of this is unavailable. In a patient maintained at 15 mg phenytoin per litre of plasma after repeated dosing, the body will contain a total of about 2 mmol of drug. The amount actually bound to albumin at a therapeutic plasma concentration is about 0.15 mmol. Even if all this were displaced, tissue drug levels would only increase by about 7.5%.

The third use described for the simulator was educational. Either drug or patient factors can be changed prior to simulating a given situation or before repeating a run. This provides a tool for pharmacokinetic experiments where hypotheses can be tested without use of animals, access to patients, or expensive analytical procedures. Organ dysfunction can be simulated and, of course, corrected during experiments. If the objective of a course is to reach 'conventional' approaches to pharmacokinetics based, for

example on the two compartment model, the simulator provides a convenient source of realistic data for analysis by students. Alternatively, and as described above, if an approach more closely integrated with physiological and biochemical concepts is desired, limited information can be supplied regarding the characteristics of a drug and its handling in the body, and students can be asked to choose appropriate factors to provide an accurate simulation.

The MacDope simulator is dependent upon a modest computer installation equipped with a type-writer keyboard and printer. However, it should rather be regarded as a very compliant patient co-operating in an infinite variety of pharmacokinetic experiments and, when killed by drug toxicity, readily re-animated.

We would like to thank Professor Giles Saunders for his interest, enthusiasm and contributions to the later development of the MacDope programme.

Address all reprint requests to:

Dr George D. Sweeney
McMaster University Health Sciences Centre
1200 Main Street West, Room 4N50
Hamilton, Ontario, Canada
L8N 3Z5

Address requests for program details to:

Dr Khursheed Ahmed
McMaster University Health Sciences Centre
1200 Main Street West
Hamilton, Ontario, Canada
L8N 3Z5

or

Dr David Ingram,
Department of Medicine (Dunn Laboratories)
St. Bartholomew's Hospital Medical College
St. Bartholomew's Hospital
West Smithfield
London EC1A 7BE
England

The program on standard magnetic tape with an operating handbook is made available and will be posted to any academic or educational institution on receipt of £100 handling charge.

APPENDIX A

LIST OF DRUG FACTORS

1. pK_A
(If a drug is neither acid or base, it is entered as an acid (factor 17 = 1) with a pK of 10).
2. Absorption rate of parenteral deposit (h^{-1})
(Inverse of the time in hours in which 63% of parenteral deposit of the drug is absorbed).
3. Lipid to water partition ratio
(This describes the fat solubility of the drug).
4. Lipid equilibration rate (h^{-1})
(The rate at which the drug equilibrates with the lipid compartment and is the inverse of the time in hours taken for 63% equilibration).
5. Intra/Extracellular distribution ratio
(Indicates how many litres of interstitial fluid are equivalent to the distribution in 1 litre of intracellular space).
6. Intracellular equilibration rate (h^{-1})
(Rate of equilibration with intracellular space, and is the inverse of the time in hours for 63% equilibration).
7. Intestinal absorption rate (h^{-1})
(Inverse of the time in hours taken to absorb 63% of the non-ionized part of the drug from the small intestine).
8. Portal transfer ratio (0–1)
(Indicates what fraction of the drug is let through the liver on the first passage through the portal system).
9. Renal tubular permeability (l/h)
(Amount of solution of the non-ionized drug which is diffused back per hour).
10. Maximum plasma binding capacity (mmol/g)
(This indicates how many mmol of drug can maximally be bound by 1 g of the plasma protein specified—see factor 38).
11. Plasma binding constant (l/mmol)
(Inverse of plasma protein concentration at which 50% of a very small drug concentration would be bound).
12. Usual administration route
(Unrestricted = 0, oral only = 1, Parenteral only = 2).
13. Maximum usual dose (mg)
(Largest dose that is usually recommended for a 70 kg man).
14. Minimum usually available oral dose (mg)
(one half of the smallest commercially available tablet).
15. Interstitial partition ratio
(Indicates how many litres of plasma are equivalent to 1 litre of interstitial space in terms of drug binding).

16. Interstitial equilibration rate (h^{-1})
(The inverse of time in hours taken to reach 63% equilibrium with the interstitial space).
 17. Index specifying if the drug is acid (1) or base (0)
(Specify pK by factor 1 above).
 18. Graph median scale or mean therapeutic level (mg/ℓ)
This determines the scale on the graphical display. The scale will be adjusted such that the graph median occurs at the first of the three decades available on the print line).
 19. 50% lethal level (mg/ℓ)
(Level at which roughly 50% of people given the drug would die).
 20. Rate of destruction by gastric acid (h^{-1})
(Inverse of time in hours taken for 63% destruction of the drug in the stomach).
 21. Gastric absorption rate (h^{-1})
(Rate at which the non-ionized part of the drug is absorbed from the stomach—inverse of the time in hours taken to absorb 63%)
 22. Toxic level (mg/ℓ)
(Drug level at which toxic reactions are likely).
 23. ' $V_{\max}$ ' of liver enzymes (mg/h)
 24. Liver enzyme association constant, $1/K_m$, (ℓ/mg)
 25. Liver conversion rate into new drug (h^{-1})
(Rate at which the drug is converted into a pharmacologically active metabolite through the liver, assuming normal liver function—inverse of the time in hours to convert 63%).
 26. ' $T_{\max}$ ' of the renal secretory mechanism (mg/h).
 27. Renal secretory association constant (ℓ/mg).
 28. ' $T_{\max}$ ' of renal reabsorptive mechanism (mg/h).
 29. Renal absorption association constant (ℓ/mg).
 30. Hepatic enzyme induction factor ($\ell/\text{mg h}$)
(If the drug has no enzyme-inducing capacities this factor is 0, otherwise a first order rate constant).
 31. Renal secretory inhibition factor, non-competitive (ℓ/mg).
 32. Renal reabsorptive inhibition factor, non-competitive (ℓ/mg)
 33. Diuretic factor (ℓ/mg).
 34. Drug dissolution time (h).
(Time for a tablet to dissolve completely in G.I. tract).
 35. Route for product of first order liver metabolic process
(0 = Product not described, 1 = Pass to plasma, 2 = Pass through entero-hepatic delay line).
 36. Drug name code of product of saturable liver metabolic process.
 37. Drug code of metabolic product.
(This gives the serial drug code number (factor 51) of a drug in MacDope which appears as a metabolite of the specified drug).
 38. Type of plasma protein binding, if present.
(This has a value 1, 2 or 3, depending upon the main plasma protein fraction to which this drug binds).
 39. Type of interaction with a liver enzyme system.
(No liver degradation = 0; Non-specific microsomal system = 1; Additional enzymes in pathways of intermediary metabolism = 2–9; Otherwise a number larger than 10 can be specified to define other enzyme systems which can be subject to competitive inhibition by drugs or metabolites).
 40. Renal secretory system type
(No active secretion = 0; Weak organic acid = 1; Weak organic base = 2; Others = 3–9; Otherwise a number larger than 10 can be specified to define some other system).
 41. Renal reabsorptive system type
(Same as above).
 42. Site of toxic reaction
(Plasma = 0; stomach = 2, intestine = 3; intestinal space = 7; intracellular space = 8).
 43. Site of lethal reaction
(Same as above).
 44. Molecular weight.
 45. Route code for product of saturable liver metabolism
(0 = Dump drug; 1 = Pass metabolite to plasma; 2 = Pass through entero-hepatic delay line to intestines).
 - 46–50 Unassigned numbers (For future use).
 51. Drug serial code number.
 52. Drug name code number
(Unique for each drug, calculated by adding codes for the letters in the drug name—see subroutine 'MXSCN'. Any currently unacceptable name code is given a (negative) error number if you try to prescribe it).
- The rates in factors 2, 4, 6, 7, 16, 20, 21, 25 are first order rate constants in h^{-1} .

APPENDIX B

PATIENT FACTOR LIST

1. Gastric emptying rate (h^{-1})
(The inverse of time it takes for the stomach to change 63% of its content).
2. Gastric pH
(Rather than the average pH in the various compartments the pH at the exchange surfaces has

to be taken. The pH of the stomach has to be set higher than the pH of the gastric contents because of the buffering capacity of the mucus in the stomach wall, etc.).

3. Plasma albumin concentration (g/100 ml).
4. Volume of fast plasma compartment (l). (This is the volume of the fast perfused space which means that this plasma volume would mix with an intravenously injected drug within one minute).
5. Lipid compartment size (Weight of the subjects's fat) (kg).
6. Interstitial fluid compartment size (l).
7. Intracellular fluid compartment size (l).
8. Hepatic enzymatic catabolic function (Gives the ratio to normal of hepatic function as compared with a normal man of 70 kg. This allows one to simulate various degrees of hepatic dysfunction).
9. Glomerular filtration rate (l/h) (7.5 l/h corresponds to 120 ml/min).
10. Urine pH.
11. Urine output (l/h).
12. Renal tubular excretory function (Gives the ratio to normal or renal tubular excretory function as compared to a normal 70 kg man).
13. Small bowel volume (l).
14. Plasma globulin 1 fraction concentration (g/dl).
15. Ratio of body weight to (standard) 70 kg (Used for estimating maximum recommended dose).

16. Intestinal motility rate (h^{-1}) (Describes the rate of intestinal emptying, i.e. the inverse of the time taken for the intestine to change 63% of its content).
17. Renal tubular reabsorptive function. (Gives the ratio to normal of renal tubular reabsorptive function as compared to a normal 70 kg man).
18. Plasma globulin 2 fraction concentration (g/dl).
19. Blood pH.
20. Volume of liver compartment (l) (Volume of slowly perfusing plasma which is that part of plasma that takes significantly longer than one minute to mix with an intravenously injected drug).
21. Gastric volume (l). (The fasting mean residual gastric volume of the subject).
22. Small intestine pH. (Of reabsorptive surface—see comments on factor 2 above).
23. Rate of equilibrium of liver compartment (h^{-1}) (Defined in terms similar to the gastric motility factor 1, above, i.e. the inverse of the time in hours reduce by 63% the difference between liver and plasma spaces).

The rates in parameters 1, 16, 23 are first order rate constants in h^{-1} .

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