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General Review

Physiologically Based Pharmacokinetic Models for Anticancer Drugs

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Summary. *The rationale and history of the development of physiologically based pharmacokinetic models are briefly reviewed in this paper. The methods of model construction and the previous application of this type of model to anticancer drugs are discussed.*

Future research should be focused on the following areas: (1) interspecies scaling, (2) the effects of disease states on the pharmacokinetics of anticancer drugs, and (3) the applications of pharmocokinetics to the studies of growth behavior of cancer cells. The ultimate goal will be to utilize this basic information to design an optimal dosage regimen and treatment schedule for the safe and effective cancer chemotherapy of each individual patient.

Introduction

The extreme toxicity of many cytotoxic drugs used in the treatment of malignant disease poses a difficult problem for the oncologist. The failure of plasma drug concentration histories to predict the proper drug concentration either in the target tumor or in the afflicted healthy tissues has often hindered the effective use of these agents. As the use of anticancer drugs increased rapidly over the past two decades, it became clear that a localized and quantitative method of predicting drug concentrations in the various parts of the human body was necessary to provide the optimal dosing schedule for cancer chemotherapy treatment.

Pharmacokinetics is defined as the study of the time course of a drug and its metabolite levels in different fluids, tissues, and excreta of the body, and of the mathematical relationships required to develop models to interpret such data. It can, therefore, provide the basic information regarding drug distribution, availability, and the resulting toxicity in the tissues and, hence, specify the limitation in the drug dosage for different treatment schedules and different routes of drug administration. The ultimate goal of the pharmacokinetic studies of anticancer drugs is thus to offer a framework for the design of optimal therapeutic dosage regimens and treatment schedules for individual patients.

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Background

Classic pharmacokinetics can be defined as the statistical curve-fitting of plasma and urine drug concentrations for individuals or a collection of individuals, using one- or multi-compartment model system. The models are based on the assumption of linear transport of the drug and its metabolites between the central compartment, which usually represents the plasma and all well-perfused tissues, and one or several peripheral tissue compartments. Due to the limitation of this 'black-box' approach, usually no representation more complicated than a three-compartment model is justified to describe the time course of the drug disposition in the body. Several excellent texts by Gibaldi and Perrier (1975) and Wagner (1971, 1975) give extensive treatment of the mathematical and conceptual foundations of classic pharamcokinetics.

The major difficulty of classic pharmacokinetics is that in almost all instances, the compartments, and their associated volumes and transfer rate constants have no anatomic or physiologic significance. Moreover, these models are species- and drug-dependent in the sense that the number of compartments and the tissues in each compartment depend on the distribution, elimination, and protein-binding characteristics of the drug. The only method of determining the number of the compartments is generally the statistical test to choose the simplest model to describe the experimental data (Boxenbaum, 1974), rather than physiologic justification.

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Although the physiologic interpretation of the information obtained from the classic compartmental approach is intrinsically limited, these models are useful for the prediction of plasma levels of the drug and for the design of therapeutic dosing schedules and dosage regimens (Wagner, 1975). However, these models have a limited ability to predict drug concentrations in different tissues or specific organs. Thus, this compartmental approach is useful in the implementation of dosage design only when the clinical response has a good correlation with the plasma drug concentrations and when the drug has a high therapeutic index in a situation where explicit concern about toxicity and tissue drug levels is not necessary. For these drugs, variation between plasma and tissue concentrations are not crucial, and with the good concentration-response correlation the plasma concentration will consequently be sufficient to project the course of the drug disposition and its response.

In contrast to most drugs that have high or moderate therapeutic indices, most of the antineoplastic drugs are very toxic and have a low therapeutic index, which requires that the concentrations of the drug be known accurately in both tumor and normal tissue to minimize healthy tissue damage while maximizing tumor kill. The pharmacokinetic requirements for cancer chemotherapy application are thus quite specialized and rather demanding. Quantitative cytotoxicity can be estimated only if the drug availability in the target is known, and careful monitoring of the drug disposition is necessary to avoid excessive toxicity to the patient. Unfortunately, monitoring the plasma drug levels to avoid toxicity is not an adequate technique, because it is well known that drug concentrations in various organs in the body are often quite different from the levels that occur in the plasma. A schematic illustration of this discussion is shown in Fig. 1. Two curves are shown, which represent the concentrations of the drug as a function of time in different compartments in the body. Curve A is the drug concentration in the plasma and this information is available to the physician simply by a sequence of blood tests. Curve B can represent the concentration either in the tumor or in a healthy organ or tissue mass. As an example, an arbitrary limit has been set, as shown by the dotted line, which is the concentration of the drug at which cytotoxic activity begins against the tumor or in the healthy tissue. The point of the figure is to show that the drug availability, CXT, or the shaded area under the concentration curve, will be quite erroneous if one uses the plasma drug concentration. This is true both from the point of view of the cytocidal activity at the tumor site (the area under the tumor curve) and from that of toxicity if the curve represents the healthy tissue. Thus, to optimize tumor kill while minimizing toxic effects, pharmacokinetic models must be able to predict, for a given dosage regimen and route of administration, the concentration of the drug in the different organs in the body as a function of time. It is clear that only a quantitative pharmacokinetic model that is based on the physiologic reality can have that predictive capability.

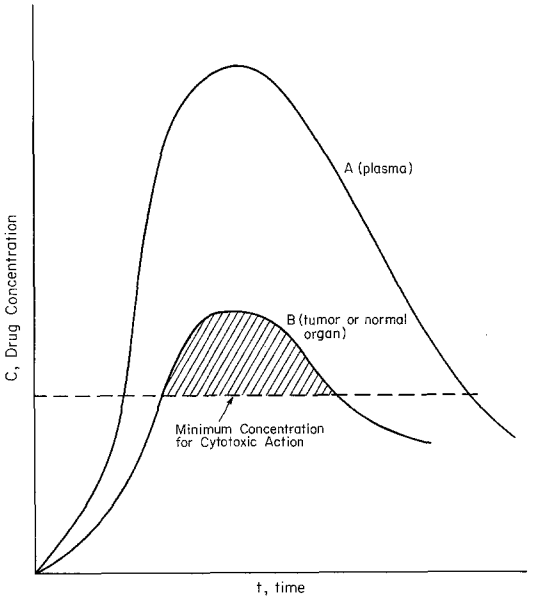

Fig. 1. The time course distribution of a drug in plasma and normal organ (or tumor)

Pharmacokinetic models that utilize the physiologic parameters such as volume of the organs or tissues and the blood flow rates through these organs were first developed by Bischoff and Brown (1966) and by Bischoff (1967) to describe the distribution of drugs in mammals. Recently the model has been applied successfully to predict the pharmacokinetics of anticancer drugs, such as methotrexate (Bischoff et al., 1970, 1971; Zaharko et al., 1971, 1972, 1974; Dedrick et al., 1973b; Lutz et al., 1975) and adriamycin (Harris and Gross, 1975), etc. A list of the anticancer drugs that have been successfully modeled is given in Table 1.

Details of the model construction will be outlined in the next section.

Model Development

A physiologic pharmacokinetic model for the distribution, disposition, and excretion of a given anticancer drug and its metabolites is illustrated in Fig. 2. The model consists of several compartments, which represent real organs or anatomic tissue regions in the body where the drug is distributed or metabolized. Use of the compartments to represent anatomic elements of the body allows inclusion of the actual blood flow rates and physiologic volumes as well as terms to describe metabolism of the drug, urinary, and biliary clearances for the

Table 1. Drugs simulated in physiologically based pharmacokinetic models

Drug classification	Name of drug	Subjects studied	References
Anticancer drugs	Actinomycin D	Beagle dog	Lutz et al., 1977b
	Adriamycin	Rabbit, human	Harris and Gross, 1975
		Human	Chan et al., 1978
	Ara-C	Mouse, monkey, human	Dedrick et al., 1972, 1973a
		Mouse	Morrison et al., 1975
		Human	Dedrick et al., 1978
	Cyclocytidine	Human	Himmelstein and Gross, 1977
	Cis-platinum	Dog	LeRoy et al., 1978
	Mercaptopurine	Rat, Human	Tterlikkis et al., 1977
	Methotrexate	Mouse, rat, dog	Bischoff et al., 1970, 1971
		Human	Zaharko et al., 1971
		Fish	Zaharko et al., 1972
		Dog	Lutz et al., 1975
		Rat	Dedrick et al., 1973b
		Mouse	Zaharko et al., 1974
		Human	Dedrick et al., 1978
Other drugs	Cephalosporin	Human	Greene et al., 1978
	Chloride	Cat	Gabelnick et al., 1970
	Digoxin	Rat	Harrison and Gibaldi, 1977a
		Dog, human	Harrison and Gibaldi, 1977b
	Halothane	Human	Zwart et al., 1972 Ashman et al., 1970 Munson et al., 1973 Smith et al., 1972
	Lidocaine	Monkey, human	Benowitz et al., 1974a and b
	Methohexital	Human	Gillis et al., 1976
	Salicylate	Dog	Chen et al., 1978
	Sulfobromophthalein	Rat, human	Montandon et al., 1975
	Thiopental	Dog, human	Bischoff and Dedrick, 1968 Dedrick and Bischoff, 1968
		Human	Gillis et al., 1976
		Dog	Chen and Andrade, 1976
	Pentobarbital	Human	Dedrick and Bischoff, 1968
	Polychlorinated biphenyls	Rat	Tuey and Matthews, 1977 Lutz et al., 1977a Anderson et al., 1977

drug and its metabolites, plasma protein, and tissue binding of the drug. A differential equation is then written for the conservation of mass of the drug in each compartment. The time course of the drug concentrations in all the compartments can be obtained by solving the set of differential equations for all the compartments numerically.

In principle, if all the parameters that can affect the disposition of the drug are taken into account, the model should be able to predict the results for in vivo experiments. However, because of the complexities of the biological systems, many assumptions are necessarily imposed, either to simplify the model or because of the paucity of data. The most common assumptions currently used are:

The model is flow-limited, which menas that the drug concentrations in the arterial blood rapidly reach equilibrium with the drug levels in the tissue space of each compartment. For this assumption to be valid, the diffusion time for the drug to cross the tissue cell membrane and enter the tissue space has to be relatively fast in comparison with the transport of the drug by the blood. As a consequence, the tissue concentration is propor-

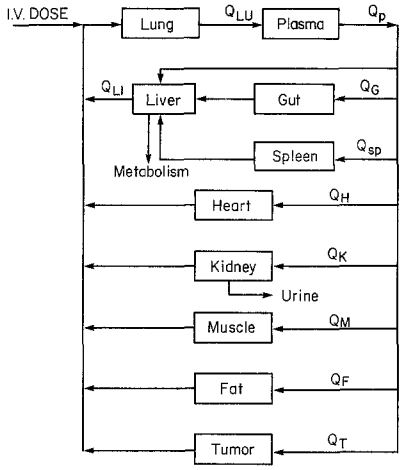

Fig. 2. Pharmacokinetic model for drug disposition

tional to the outgoing venous drug concentration, and the total concentration of the drug in any particular compartment can be expressed as its venous plasma drug level multiplied by a constant R. This constant R is called the partition coefficient or the distribution ratio of the drug between the tissue and plasma.

The plasma protein binding and the tissue binding are assumed to be linear. Under this assumption, the R values for all the compartments will be constant and independent of the concentration of the drug.

The concentration of the drug in any given compartments is homogeneous. For well-perfused organs such as liver, heart, and kidney this is usually the case. However, for organs like skin and lean tissues, which are poorly perfused, this assumption is only a first-order approximation.

With the above assumptions, the governing differential equation for the time history of the drug concentration in a typical compartment is then

$$V\frac{dC}{dt} = QC_p - Q\frac{C}{R} - K\frac{C}{R} - \frac{V_m C}{K_m + C} \tag{1}$$

where C and C_p are the drug concentrations in the compartment and in the plasma, respectively. V and Q are the volume and blood flow rate in that compartment. K is the apparent first-order clearance rate and V_m and K_m are the Michaelis-Menten constants for the metabolism of the drug in that compartment. Equation (1) states that the rate of change of the amount of drug in the compartment is equal to the difference between the amount entering the compartment (QC_p) and the amount leaving the compartment by convection (QC/R), elimination (KC/R), and metabolism ($V_mC/[K_m + C]$).

Solution of the set of differential equations requires that the parameters used first be determined. The organ volume V and the plasma flow rate Q are obtained from the physiologic values for the subject to be simulated. The rate of clearance, which is usually the kidney clearance, is estimated by plotting the cumulative amount of the drug in the urine against the area under the plasma drug concentration curve for a given time. K, the first-order clearance rate, is then taken as the slope of this line. An alternative method is to calculate the clearance from

$$K = \frac{\text{total urinary excretion}}{CXT} \tag{2}$$

where CXT is the area under the plasma concentration curve from time zero to the time of last urine collection.

The metabolic rate constants V_m and K_m are usually estimated from in vitro experiments. If the in vivo concentration of the drug is in the linear range of the metabolism curve ($C \ll K_m$), the nonlinear term in Eq. (1) can be further simplified to a first-order metabolic elimination.

The distribution ratios, R, are generally obtained from animal experiments. After the administration of the drug, the animals are sacrificed at given time points and the drug concentrations in plasma and various organs and tissues are measured. If the drug is administered by constant rate infusion, the tissue-to-plasma ratios are equal to R for noneliminating compartments at steady state (Chen and Gross, 1979). For organs that have elimination, the rate of clearance has to be taken into consideration and

$$R = \left(1 + \frac{K}{Q}\right) \cdot (\text{tissue-to-plasma ratio at steady state}). \tag{3}$$

If the drug is administered by IV bolus injection, further correction to R may be important (Chen and Gross, 1979).

Once the R values are obtained from the particular animal, the pharmacokinetic model for that animal can be constructed. To allow the use of the same model for another species, the assumption that the R values remain the same from one species to another has to be imposed. It should be noted that this assumption is not always true. For example, the distribution of digoxin in rat is different from that in dog and human. Thus, Harrison and Gibaldi (1977a and b) had to use the distribution ratios for dog in their simulation for the disposition of digoxin in human. However, if the model successfully simulates the plasma and urine data in human, the assumption that R values remain unchanged between the animal and human is probably true.

Another point that should be noted is the route of drug administration. When given by IV bolus injection or constant-rate infusion, the drug enters the lung compartment directly. In the case of IA injection, the drug enters the plasma compartment. If the lung compartment is excluded from the model, there will be no difference between the IV and IA injection, since the drug is then always given into the plasma compartment. To simulate the IP administration of a drug, an additional compartment for the peritoneal cavity has to be included and the drug is injected directly into this cavity (Dedrick et al., 1978). No model has been proposed for the oral administration of a drug, probably due to the difficulties in the estimation of gastrointestinal absorption rate constant k_a and the drug availability F. If these two parameters can be estimated independently, one should be able to simulate the drug concentrations by giving the drug into the gut (or stomach) compartment with an absorption function equal to $FDK_a \cdot \exp(-k_a)$, where D is the dose of the drug.

For readers who are interested in the details and procedures needed to construct pharmacokinetic models based on physiologic, physicochemical, and pharmacologic principals, the paper by Bischoff (1975) is recommended.

Models of Anticancer Drugs

Actinomycin D

A flow-limited pharmacokinetic model was presented for the distribution of actinomycin D in beagle dog (Lutz et al., 1977b). Linear binding of the drug to tissues and linear kidney and biliary clearances were assumed for this drug. At doses of 0.6 mg/m^2 (0.03 mg/kg) and 2.7 mg/m^2 (0.135 mg/kg), the model provided good simulation of the experimental data for most normal tissues, e.g., plasma, liver, muscle, small intestine, etc. (Fig. 3). This indicates that the kinetics assumptions used for the model of actinomycin D are most likely to be correct.

However, for the testis compartment, the drug concentration data (Fig. 4) do not parallel the declining plasma curve as the rest of the tissues do. A linear membrane-limited model with a diffusion parameter k of 0.2 h^{-1} for both doses was then used to obtain a reasonable simulation of the data. In general, the transport of drug is membrane diffusion-limited only if the diffusion parameter, k, is much smaller than the tissue perfusion rate per unit volume, Q/V (Dedrick and Bischoff, 1968; Dedrick et al., 1975). In the case of actinomycin D in the testis, Q/V = 15 h^{-1}, which is much faster than the value for k (0.2 h^{-1}) determined with the model. This suggests that there is a significant barrier that limits the rate of actinomycin D uptake by the testes.

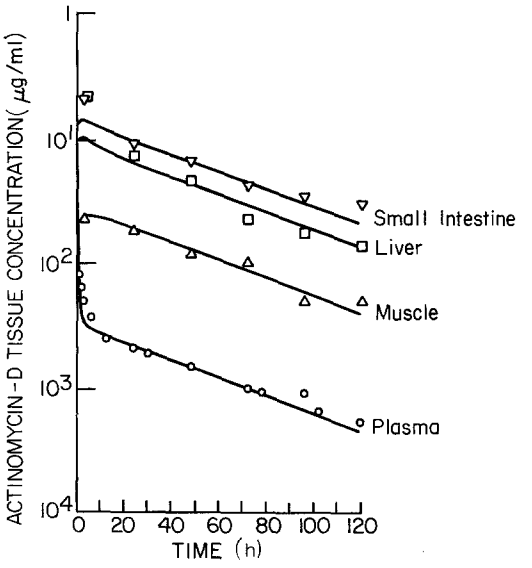

Fig. 3. Tissue concentration vs. time for actinomycin D in the beagle dog following a 0.6-mg/m^2 (0.03-mg/kg) IV dose. *Points* represent experimental data. *Solid lines* represent simulations using the flow-limited model. Lutz et al., 1977b

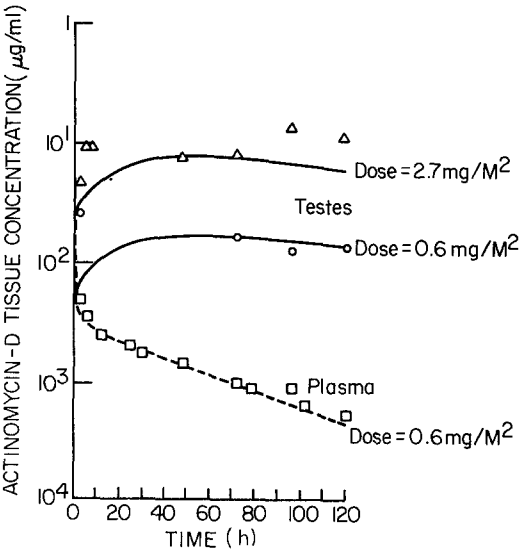

Fig. 4. Testes concentration vs. time for actinomycin D in the beagle dog at 0.6-mg/m^2 (0.03-mg/kg) and 2.7-mg/m^2 (0.135-mg/kg) IV doses. *Points* represent experimental data. *Solid lines* are simulations for testes using the membrane model with k = 0.2 h^{-1}. *Dashed line* is plasma simulation for 0.6 mg/m^2 only. Lutz et al., 1977b

Adriamycin

The pharmacokinetic model for the disposition of adriamycin in rabbit was developed by Harris and Gross (1975). The model was also flow-limited with the first-

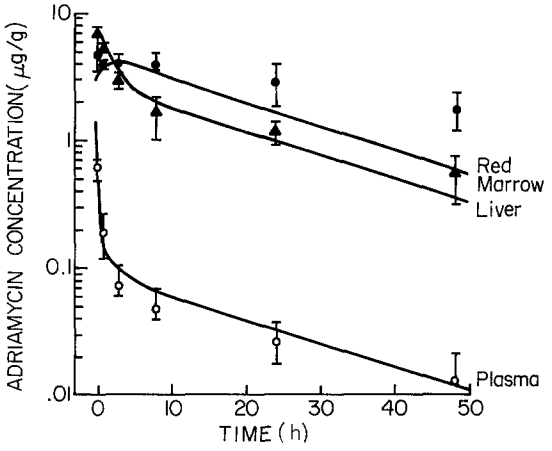

Fig. 5. *Continuous curves* represent computer-generated predictions of adriamycin in the indicated compartment based on the model after a 3-mg/kg IV injection of adriamycin. *Point symbols* represent actual tissue concentrations of adriamycin after a 3-mg/kg IV injection in rabbits. The range of these concentrations is represented by the *I bars*. ● = marrow; ▲ = liver; ○ = plasma concentrations. Harris and Gross, 1975

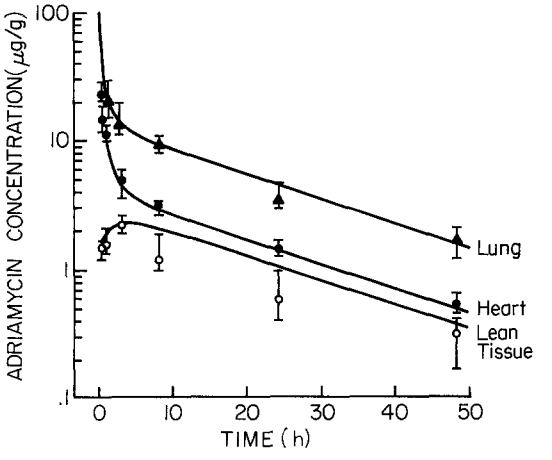

Fig. 6. Same as Fig. 5, but ▲ = lung; ● = heart; ○ = lean tissue concentrations. Harris and Gross, 1975

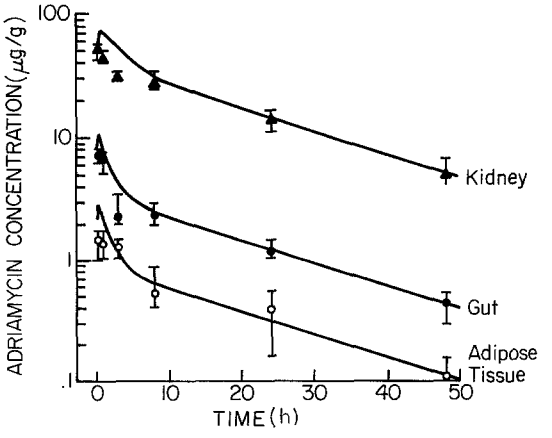

Fig. 7. Same as Fig. 5, but ▲ = kidney; ● = gut; ○ = adipose tissue concentrations. Harris and Gross, 1975

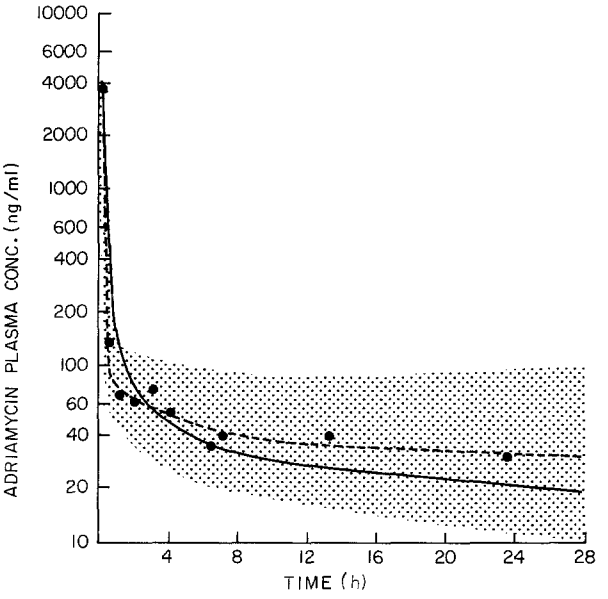

Fig. 8. Nonlinear curve fit (*broken line*) of adriamycin plasma concentration data to a three-compartment open model in a patient. The *shaded area* indicates ± 1 SD of the fit. The model predicted plasma time course is also shown (*solid line*). Chan et al., 1978

order elimination of the drug occurring at the liver compartment. A 50% plasma protein binding was used in the simulation. The results for 3-mg/kg IV injection of adriamycin in rabbits agreed with the experimental data very well (Figs. 5—7). However, when the model was used to simulate the adriamycin plasma concentrations in a human patient after a 60-mg/m^2 IV dose (Chan et al., 1978), the agreement was reasonably good (Fig. 8). This may indicate that other factors, such as nonlinear metabolism of the drug and the binding affinity of human tissues, play no important role.

Cis-Dichlorodiammine-Platinum (DDP)

A physiologic pharmacokinetic model for the disposition of DDP in the beagle dog has recently been developed by LeRoy et al., (1978). The model was flow-limited and all the parameters were determined on the basis of the in vivo distribution of total platinum in organs, tissues, and body fluids of dogs. On the basis of the in vitro binding experiments indicating that the increase of binding was independent of the concentration of the drug, DDP was assumed to be rapidly cleared and not bound to plasma protein. The prolonged terminal half-life of DDP was assumed to be due to the metabolites, which were cleared much more slowly and were 92%—95% bound to plasma protein.

The results for the simulation of a single IV dose of 1 mg/kg in dog agreed very well for the *total* platinum

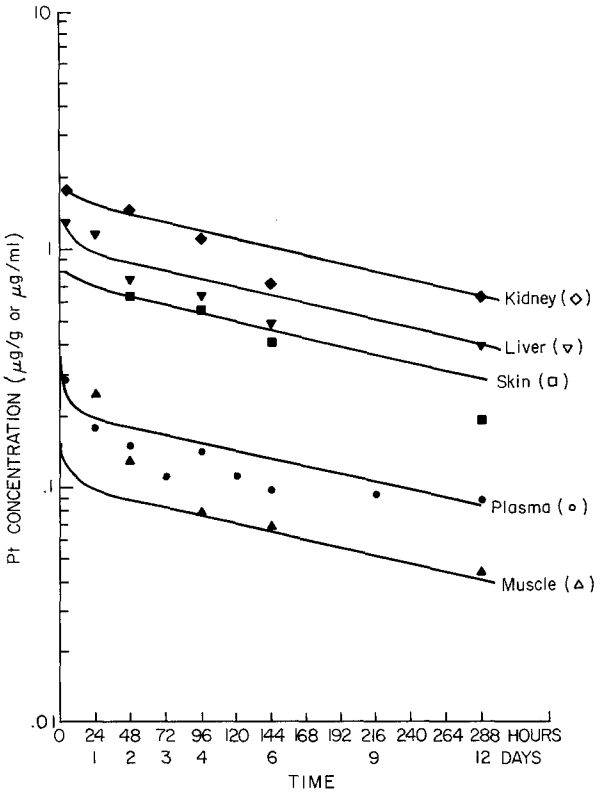

Fig. 9. Platinum concentration as a function of time for 12 days after a single IV dose of 1 mg DDP/kg in the dog. *Solid curves* represent model simulations. LeRoy et al., 1978

concentrations. The concentrations of DDP in various organs are shown in Fig. 9 and are compared with the model simulation. It should be noted that the drug concentration in the kidney is about one order of magnitude higher than the plasma concentration. This might help explain the clinically observed kidney toxicity in humans due to DDP. Implementation of this model for the disposition of DDP in humans could help the design of regimens to avoid severe nephrotoxicity. However, although the model also predicted the concentrations of DDP and its metabolites at any given time, no measurements or comparisons were presented. Since only the free drug (DDP) is active, more data are required to further verify the model.

Cyclocytidine

Himmelstein and Gross (1977) presented a model for the pharmacokinetics of cyclocytidine in humans. The model was flow-limited, with metabolism in the heart, liver, and kidney compartments. Kidney clearance was linear and the hydrolysis kinetics of the drug obtained from in vitro data were assumed to take place in all the tissues. The results of model prediction and the experimental data agreed reasonably well.

Cytosine Arabinoside (Ara-C)

The pharmacokinetic model for the disposition of Ara-C (Dedrick et al., 1972) was one of the first physiologic models developed for anticancer drugs. The model successfully took account of the metabolism and deamination of Ara-C into Ara-U in vivo by utilizing the enzyme activities and Michaelis constants determined in vitro. The model prediction of the distribution and disposition of Ara-C and Ara-U in man agreed very well with the in vivo experimental results. The deamination of Ara-C into Ara-U in mice, monkeys, dogs, and humans were later studied by means of this model (Dedrick et al., 1973a).

More recently, the disposition and distribution of this drug and its metabolites were also studied by Morrison et al. (1975). The original model developed by Dedrick et al. (1972) was extended by adding another compartment and including more metabolic details. The parent drug Ara-C and its metabolites Ara-U and Ara-CTP were simulated simultaneously and shown to be in agreement with the experimental measurements for both blood levels of Ara-C and tissue levels of Ara-CTP as a function of time (Table 2). Since Ara-CTP is the metabolite of Ara-C that kills dividing cells and also inhibits the rate of DNA synthesis, the agreement of Ara-CTP concentration simulation with experimental data is highly significant, because the antitumor activity of a single injection of Ara-C can then be quantified and predicted. This pharmacokinetic model was recently incorporated with intracellular enzyme kinetics and cell kinetics to simulate the treatment of L1210 leukemia by Ara-C (Lincoln et al., 1976).

Table 2. Simulation results for DBA mouse at 60 min, 2.5 mg/kg. Morrison et al., 1975

Organ		Ara-C	Ara-C + Ara-U	Ara-CTP
Blood	(S)	1.10	1.44	0.0
	(E)	–	1.44	0.02
Liver	(S)	1.12	1.52	0.21
	(E)	1.36	1.45	0.22
Spleen	(S)	1.14	1.50	1.34
	(E)	–	2.05	1.26
Kidney	(S)	0.50	0.72	0.003
	(E)	–	1.50	0.05
Intestine	(S)	1.11	1.50	0.03
	(E)	–	1.65	0.46

S = simulation; E = experimental; units are μm

Methotrexate (MTX)

Methotrexate was the first anticancer drug to be studied by means of a physiologic pharmacokinetics model (Bischoff et al., 1970) and remains the most studied of the anticancer drugs. The preliminary model was developed by Bischoff et al. (1970) and was subsequently modified by Bischoff et al. (1971) and Zaharko et al. (1971). The model was flow-limited with nonlinear binding and included enterohepatic recycling. Agreement between predictions and experimental results was excellent for concentrations of MTX over several orders of magnitude (Fig. 10).

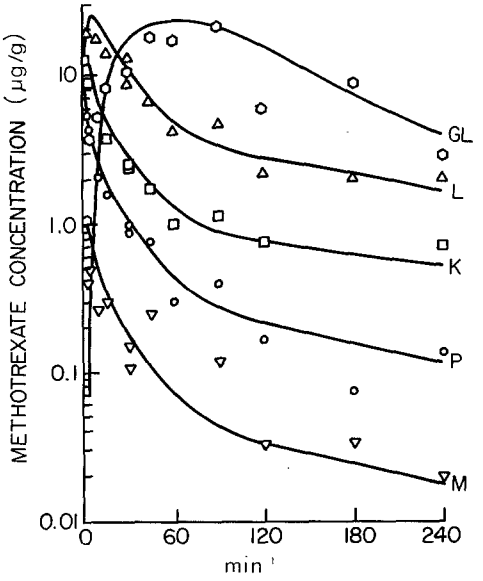

Fig. 10. Model prediction vs. experimented results in mice with 3 mg/kg IV. *Solid lines* are model predictions; *symbols* are experimental data. GL (○) = small intestine; L (△) = liver; K (□) = kidney; P (○) = plasma; M (▽) = muscle. Bischoff et al., 1971

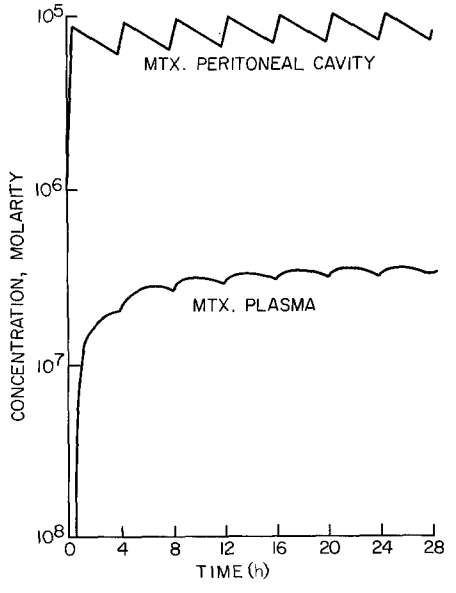

Fig. 11. Model simulations of plasma and peritoneal fluid Cs of MTX administered by repeated peritoneal lavage to 70-kg human: V = 4.5 liters (4-liter exchange); PA = 8 ml/min; k = 190 ml/min. Dedrick et al., 1978

The transport and binding of methotrexate in vivo were later studied by Dedrick et al. (1973b), who used a similar model. The model has been used more recently to describe the kinetics of MTX distribution in spontaneous canine lymphosarcoma in vivo (Lutz et al., 1975) and to study the relative toxicity of MTX in tissues of mice bearing Lewis lung carcinoma (Zaharko et al., 1974). Most recently, the same model was modified by adding a peritoneal cavity compartment for the study of IP drug administration in the treatment of ovarian cancer (Dedrick et al., 1978). Pharmacokinetic calculations indicate that for IP administration of MTX the concentration of the drug in the peritoneal space will be significantly greater than in the plasma (Fig. 11). This concentration difference offers a potential advantage in the treatment of ovarian cancer that is confined to the peritoneal cavity.

The same model for MTX was also used to simulate the pharmacokinetics of mercaptopurine (Tterlikkis et al., 1977).

Conclusions

The ultimate purpose of studying pharmacokinetics is to provide the basic information about the concentration of the drugs in the target organ at any given time as a function of the dosage and treatment schedule. From such information, the effects and responses of the drug can then be correlated, and eventually an optimal dosage regimen and dosing schedule can be designed to give a safe and effective cancer chemotherapy for each individual patient.

In the area of anticancer drugs, many pharmacokinetic models have been developed, but not much work has been done on the use of the physiologic pharmacokinetic model to predict the killing of cancer cells. The only system that has been studied successfully seems to be the treatment of L1210 leukemia with Ara-C (Bischoff et al., 1973; Himmelstein and Bischoff, 1973a and b; Lincoln et al., 1976). The time courses of the drug concentrations in various organs were predicted from the pharmacokinetics model. Together with a quantitative description of the growth and death of cancer cells as a function of drug concentration, the survival of the host was then predicted. The prediction agreed quite well with the in vivo survival data for the treatment of L1210 leukemia with Ara-C in mice. An advantage of this system is that there are extensive studies of the growth and drug-cell survival data for L1210 leukemia. For other types of cancers, the growth kinet-

ics may prove to be too complicated for a model to be developed precisely. An approximation of the cell growth behavior with a working pharmacokinetic model will still provide some insights into the complex systems.

Another area for future research lies in the study of the effects of disease states on the pharmacokinetics of anticancer drugs. The effects of renal failure and liver diseases can be studied with a predictive pharmacokinetic model that has a physiological basis. By changing the rates of kidney clearance and liver metabolism, and the blood flow rates through the kidney and liver, different diseases can be simulated and their effects on the anticancer drug disposition can then be predicted and compared with clinical studies. However, the effect of tumors on the pharmacokinetics may be more difficult to study. It is not likely that the physiology of the circulation system will be changed, but there are some indications that the distribution ratios, R, are changed due to the existence of tumor (Hoeschele and VanCamp, 1972). If this is the case, the study of anticancer drug pharmacokinetics with normal animals may be useless, and tumor-bearing animals have to be used instead.

A third application of the physiologic model will be in the area of interspecies scale-up. Since most drug toxicity studies have been conducted in animals, a physiologic pharmacokinetic model will be the best tool with which to relate and apply the abundant animal data to the treatment of human cancers. Little work has been done in this area (Dedrick, 1973), and more emphases are required in the future.

Finally, the most important application for the future is the prediction of toxicity and tumor cell kill in vivo. Dedrick et al. (1978) have made an important first contribution to the use of predictive pharmacokinetics, suggesting the use of IP injection for methotrexate in ovarian cancer. Chen and Gross (1978) have qualitatively predicted the cardiotoxicity of adriamycin in humans for different regimens. They were able to show that their predictions agreed with clinical studies and suggested that low-dose weekly regimens provide a less toxic and clinically effective protocol for adriamycin. These are first steps in the development of pharmacokinetics programs that will provide the physician with methods of designing protocols more effectively and predicting regimens for clinical trials.

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