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Pharmacokinetic Models for Lipophilic Compounds

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In many instances pharmacokinetic modeling offers the best method of interpreting the significance to man of results obtained with laboratory animals but first we must have accurate models for our laboratory animals. A physiological pharmacokinetic model has been used to simulate the disposition of polychlorinated biphenyls (PCBs) in the rat and to extrapolate results obtained with the rat to predict the disposition of PCBs in the mouse. The modeling methods have also been extended to predict the disposition of a polybrominated biphenyl (PBB) in the rat following IV, oral, and multiple oral doses. It is anticipated that with additional experience and work a physiological pharmacokinetic model can be used to predict the disposition of these and other xenobiotics in man.

Introduction

Pharmacokinetics is basically a study of those factors that determine the time concentration of a foreign compound and its metabolites in tissue following a given dose. Pharmacodynamics is the study of those factors which determine the relationship between the concentration of a foreign compound and a therapeutic or toxicological response. Both pharmacokinetics and pharmacodynamics are efforts to interpret the human relevance of data obtained in the laboratory. Therefore, an ideal study of a foreign compound should include both pharmacokinetics and pharmacodynamics. However, some environmental contaminants elicit such diffuse responses as to make pharmacodynamic studies virtually impossible. In these cases we are restricted to studies of the pharmacokinetics of these compounds if we are going to make any type of accurate extrapolation from animal data to man. This is the case with most of the halogenated hydrocarbons generally considered to be environmental contaminants. Therefore, we have committed most of our effort to understanding the pharmacokinetics of these compounds. A pharmacokinetic study is needed because, in most cases, the transformation from the dosage pattern to the concentration of the compound at the target organ is not linear and perhaps more important the toxicological or therapeutic response is not a function of concentration but depends upon the area under the concentration–time curve.

We believe the most promising approach to extrapolating data obtained with laboratory animals to man is by means of a physiological pharmacokinetic model. A physiological pharmacokinetic model has as its basis relevant physical and biochemical parameters such as blood flow rates, organ sizes, tissue binding, and metabolic rates. The model can predict tissue levels of parent compound from various types and patterns of chemical exposure. Thus, it is a simplified representation of a real biological system derived from experimental observation, previous knowledge, and a number of assumptions. A valid model for one species can be scaled to make predictions in another species if the basic mechanisms of distribution, metabolism, and excretion are the same in each case.

Polychlorinated Biphenyls

We chose to study the polychlorinated biphenyls (PCBs) because they are a major group of environmental pollutants and because we think they may serve as excellent models for the disposition of other types of environmental pollutants.

The PCBs have been used industrially since the

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1930's. They have been used in hydraulic fluids, pump oils, paints, adhesives, inks, caulking compounds, plastics, and a number of other products; however, their current use is largely restricted to the electrical industry for use in transformers and capacitors (*1*). The first cases of industrial intoxication by PCBs were described in 1936; however, due largely to the available technology and the fact that the PCBs were not looked for, they were not detected in the environment until 1966 (*2*). The first cases of human intoxication as a result of pollution occurred in Japan in 1968 when a large number of persons consumed PCB-contaminated rice oil (*3*). More recently, PCB contamination has raised concern in the U. S. because of the high concentrations in the Hudson River and the Great Lakes.

In addition to being worthy subjects of study in their own right, the polychlorinated biphenyls are representatives of the larger class of environmental contaminants, the halogenated hydrocarbons. This class of compounds contains the chlorinated insecticides such as DDT and Kepone, the polybrominated biphenyls (PBBs), and the halogenated benzenes, phenols, and naphthalenes as well as the halogenated dioxins and furans.

One additional advantage of studying the PCBs is seen from analysis of their structures. Each of the PCBs has the same biphenyl carbon skeleton, and they differ only in the degree and position of their chlorination. There are 210 possible variations, and any commercial formulation may contain 30 or more individual chlorinated biphenyls. Since it was obvious that we could not study them all, we have tried to make some careful choices.

Pharmacokinetic Model

Our preliminary results indicated that a flow limited pharmacokinetic model could be used to predict the disposition of the PCBs in the laboratory rat (*4*). The model consists of a series of compartments which represent particular tissues in which the concentration of the parent compounds and metabolites are assumed to be uniform. A basic assumption of the model is that the tissue concentrations of both the parent compounds and the metabolites are in equilibrium with the venous blood leaving the tissue. A representative compartment of the model is shown in Figure 1. The PCB enters the compartment at one concentration in the arterial blood and leaves it at a second concentration in the venous blood. The concentration change is brought about by a blood/tissue partition which is different for each tissue. The full model is shown schematically as a flow diagram in Figure 2. The time course of PCB concentration is expressed by a set of differential equations which describe the individual mass balances of both the parent compound and the metabolites in each compartment. The model equations relate the rate of accumulation (or depletion) of each compound in each compartment to the rate of influx with arterial blood minus the rate of efflux with venous blood and the rate of metabolism and excretion.

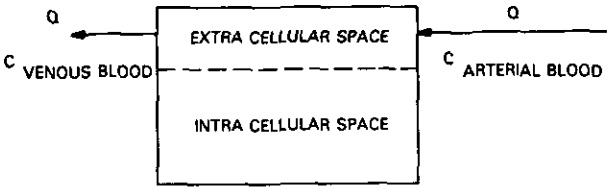

FIGURE 1. Representation of a single compartment for a flow limited model. From Lutz et al. (*4*) with permission.

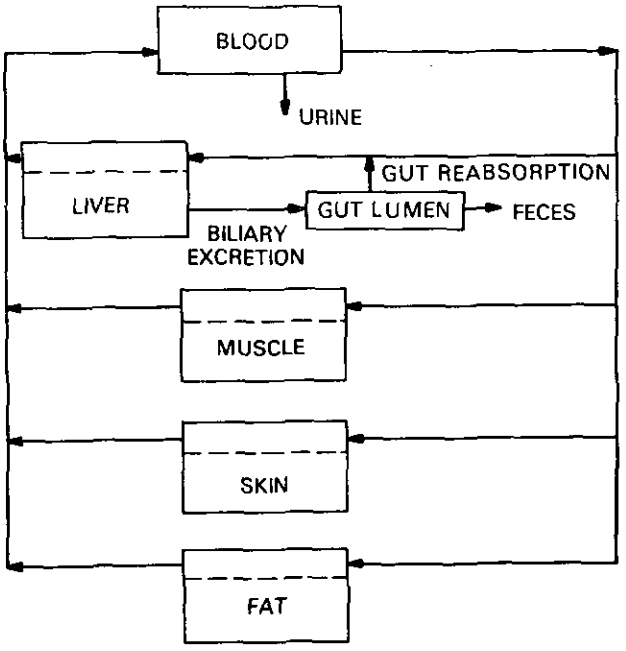

FIGURE 2. Flow diagram for a pharmacokinetic model of PCB disposition in the rat. From Lutz et al. (*4*) with permission.

This type of model requires knowledge of a considerable number of biological parameters. Where possible, the parameters were obtained from the literature; where necessary, they were determined in our laboratory. The parameters used in this model are given in Tables 1–3.

Table 1. Model parameters for a 250 g rat.

Compartment	Volume, ml	Blood flow, ml/min
Blood	22.5	—
Gut lumen	14	—
Muscle	125	7.5
Liver	10	16
Skin	40	0.5
Fat	17.5	0.4

Table 2. Tissue to blood distribution ratios for 250 g rat.

	Parent				Metabolite			
Compartment	1-CB	2-CB	5-CB	6-CB	1-CB	2-CB	5-CB	6-CB
Blood	1	1	1	1	1	1	1	1
Gut lumen	1	1	1	1	1	1	1	1
Muscle	1	2	1	4	0.14	0.40	0.10	0.30
Liver	1	3	6	12	2	5	2	4
Skin	10	10	7	30	0.25	0.30	0.10	2
Fat	30	70	70	400	0.40	0.60	0.40	2

Table 3. Kinetic parameters for a 250 g rat.[a]

Constants	1-CB	2-CB	5-CB	6-CB
k_m,ml/min metabolism constant	10.0	2.0	0.39	0.045
k_k,ml/min kidney clearance	0.20	0.133	0.033	0.030
k_B,ml/min biliary clearance	0.20	0.35	0.30	0.30
k_G, min^{-1} gut reabsorption	0.00016	0.00016	0.00016	0.00016
k_f, min^{-1} fecal transport	0.0008	0.0008	0.0008	0.0008

[a]Parameter values from Lutz et al. (4).

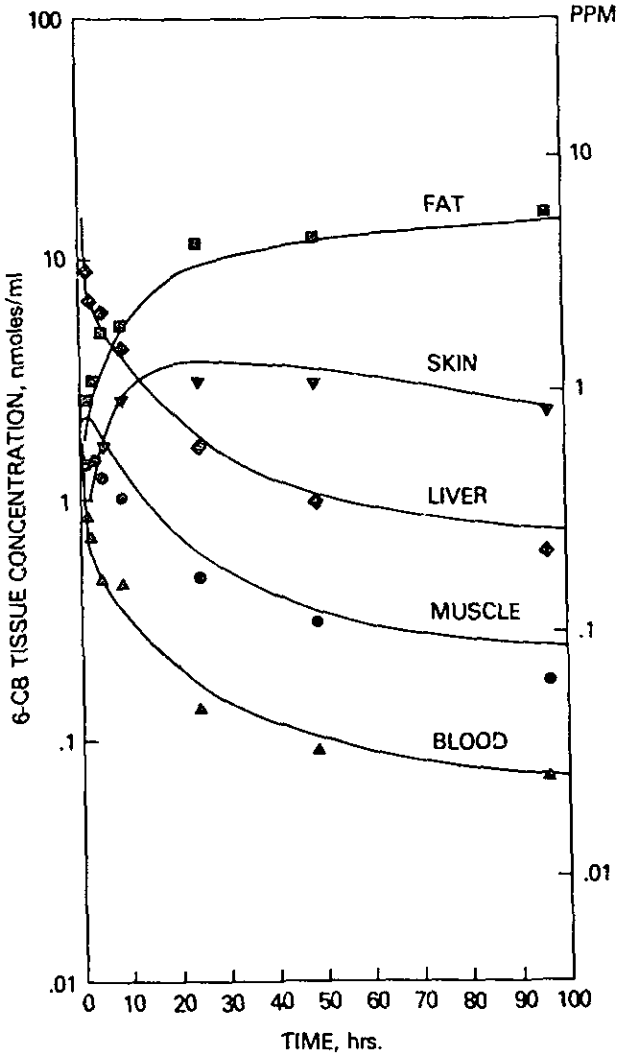

FIGURE 3. 6-CB tissue concentrations as a function of time for 96 hr after a single IV dose of 0.6 mg/kg in the rat. Points represent experimental data: solid lines represent computer simulations. From Lutz et al. (4) with permission.

Model Predictions vs. Laboratory Data

Computer simulations using the model to predict the distribution and excretion of PCBs by real animals are quite accurate for the slowly metabolized PCBs in the laboratory rat. An example is given in Figure 3, where the solid lines were generated by the computer based on the physiological parameters and assumptions of the pharmacokinetic model. These lines are not curve fits of the data points which were obtained from actual laboratory experiments following a single IV dose of 2,4,5,2′,4′,5′-hexachlorobiphenyl (6-CB). It should be noted that the ordinate is a log scale and that the concentration of 6-CB in fat and skin were much higher than in blood.

The distribution of 6-CB in the fat and blood at longer periods of time is shown in Figure 4. During the 42-day holding period shown in Figure 4, the body weight of these animals increased by approximately 50%. Much of the increase was due to an increase in adipose tissue. The dashed lines represent the model predictions when the tissue growth was ignored; the solid lines represent the predictions when the growth of the fat compartment was simulated by the model.

Thus, it is seen that the model works well for this PCB in this species. It also stimulates the distribution of all the other PCBs studied. However, this model, like most other pharmacokinetic models,

works best for those compounds for which accurate estimates of the *in vivo* metabolic rate are available. Estimates of the rate of *in vivo* PCB metabolism are most accurate for those PCBs which are metabolized most slowly. However, the lower chlorinated PCBs, those most readily metabolized, are the least persistent in the environment, and human exposure is largely restricted to those PCBs which are resistant to metabolism. This particular hexachlorobiphenyl has been reported to be in the highest concentration of any PCB found in human adipose tissue (*5*).

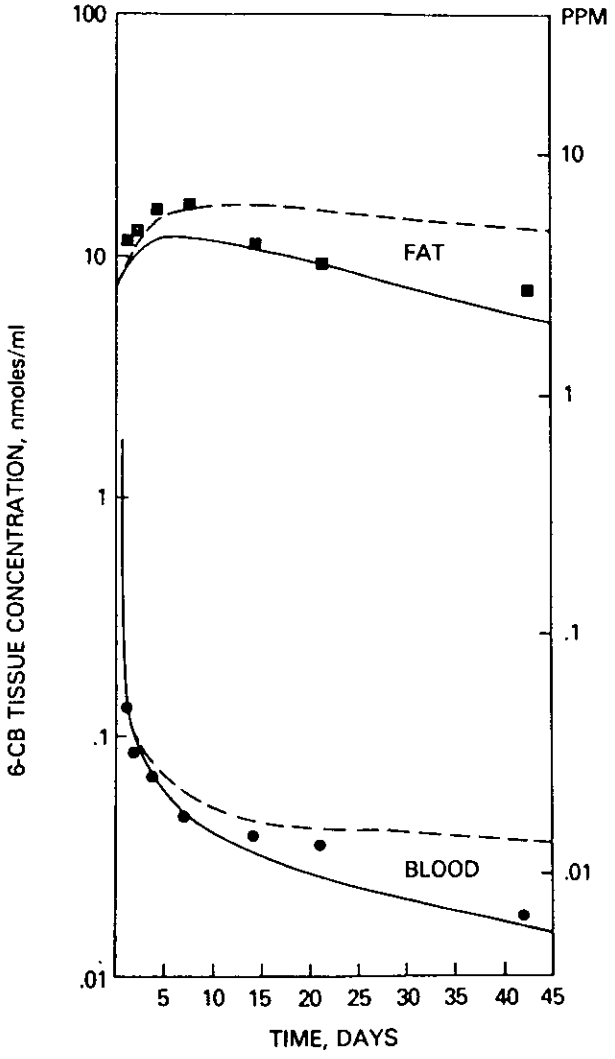

FIGURE 4. 6-CB concentration in fat and blood as a function of time for 42 days after a single IV dose of 0.6 mg/kg in the rat. Points represent experimental data; (— —) simulations with a constant fat volume; (——) simulations with an increasing fat volume. From Lutz et al. (*4*) with permission.

The idea behind studying the pharmacokinetics of environmental contaminants is to be able to extrapolate results obtained with laboratory animals to humans. We cannot do that yet, but we have taken the first step. We can extrapolate to mice. Figure 5 shows a comparison of the computer simulation and the laboratory data for the tissue distribution of this hexachlorobiphenyl in the mouse. The solid lines represent the computer simulation; the points represent the data obtained in the lab. Thus, the first small step was a solid one, and the model extrapolated to the mouse very well. We are currently in the process of obtaining the laboratory data necessary to check our simulation of PCB distribution in the dog and the monkey. If these extrapolations work as well as anticipated, we feel confident that this model can be used to make reasonable predictions of the disposition of PCBs in the humans.

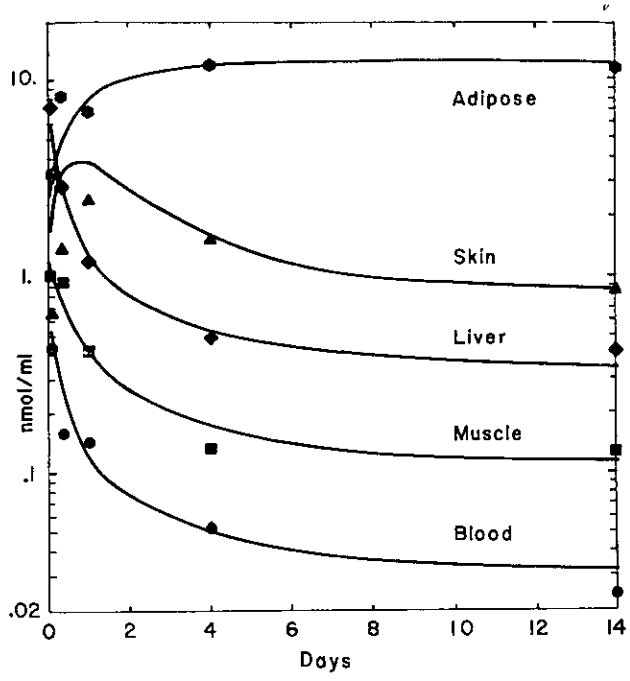

FIGURE 5. 6-CB tissue concentrations as a function of time for 14 days after a single IV dose of 0.6 mg/kg in the mouse. Points represent experimental data; solid lines represent computer simulations. From Tuey and Matthews (*7*).

In addition to being able to extrapolate our results obtained with the rat to other species, we would also like to be able to extend our results obtained with the PCBs to other halogenated hydrocarbons; and we have made a small step in that

direction. Figure 6 shows the results obtained when these pharmacokinetic methods were extended to predict the tissue concentration of a polybrominated biphenyl in the rat following a single IV dose. This particular brominated biphenyl, 2,4,5,2′,4′,5′-hexabromobiphenyl, is the major constituent of the fire retardant, Firemaster BP-6, which accidentally contaminated the livestock feed and subsequently the livestock, the animal produce, and most of the population of Michigan in 1973 and 1974 (*6*). Once again, the lines in this figure represent the computer simulation and the points represent the actual data. It is seen that the extrapolation worked quite well.

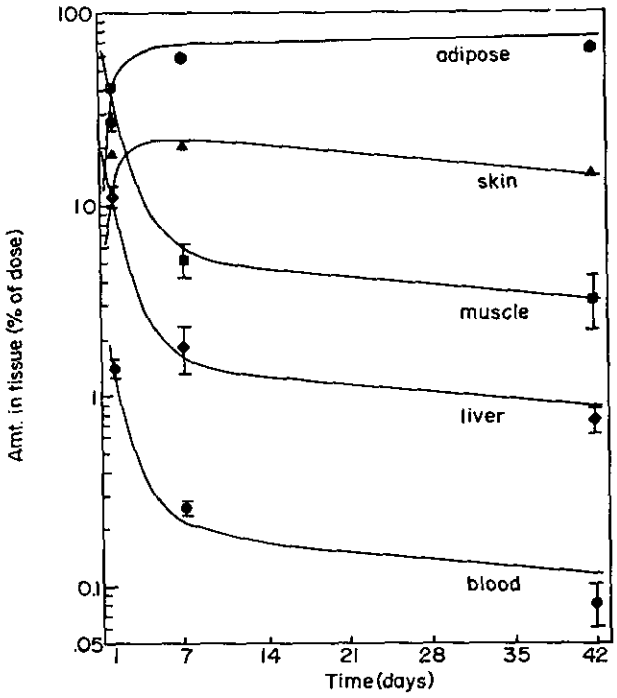

FIGURE 6. Hexabromobiphenyl disposition in the rat as a function of time for 42 days after a single IV dose of 1.0 mg/kg. Points represent experimental data; solid lines represent computer simulations. From Tuey and Matthews (*8*).

Since very few of us receive our environmental contaminants via IV injection, we have studied the disposition of multiple oral doses of the PBB and were pleased to find that our model also accurately predicted their disposition (Fig. 7). In Figure 7 the lines represent the computer simulation of PBB distribution during the administration of four consecutive daily doses, and the comparison with the data obtained when rats which had received four daily doses were sacrificed on the seventh day after the study began. The points at day 1 represent animals which were sacrificed 24 hr after receiving a single oral dose. This simulation of multiple oral doses is good, but we are currently giving the model a tougher test by simulating the distribution of up to 30 daily doses and three different dose levels. We are, of course, checking the simulation with actual data obtained in the laboratory. If this simulation and the data check out, we think we will have a pretty good model for the PBBs.

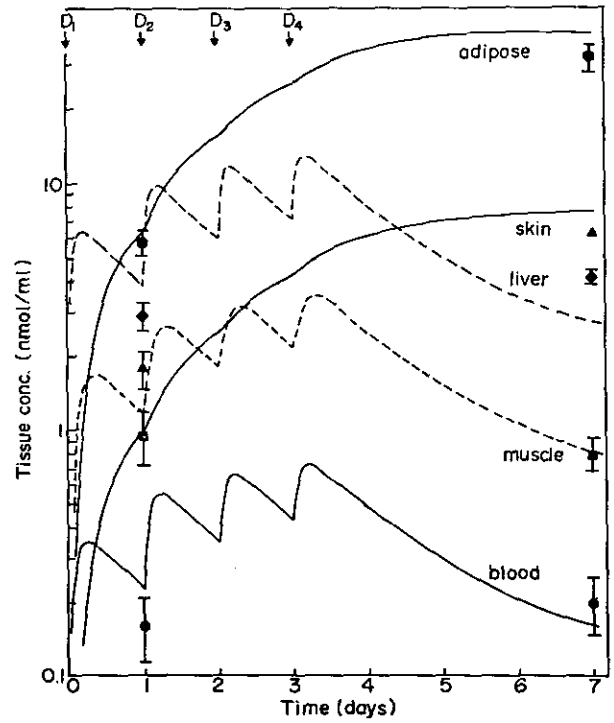

FIGURE 7. Hexabromobiphenyl disposition in the rat as a function of time after 1 or 4 oral doses of 1.0 mg/kg. Points represent experimental data; lines represent computer simulations. From Tuey and Matthews (*8*).

Conclusions

We have demonstrated that a physiological pharmacokinetic model can accurately simulate the disposition of lipophilic xenobiotics in laboratory animals. We are currently completing a model of the disposition of Kepone in the rat, and we are working to add the proper parameters to the model so that it will predict the disposition of other halogenated hydrocarbons in other species.

I should point out here, that we are not unaware that if a target organ can be identified it might necessitate additional compartments in the model to account for the toxicity which results from a long-term low dose exposure. This does not worry us —the model can handle it. The only reason the minor compartments have not been added to date is that they account for an insignificant portion of the disposition of the total dose, but they do require a great deal of work to check.

We believe that with additional experience we will be able to predict the disposition of a large number of persistent xenobiotics in laboratory animals and within the next two to three years, that is, after we have experience with a few more species, it should be possible to begin to extrapolate some of these results to humans.

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