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Development of Physiological Pharmacokinetic Model

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Abstract □ The development of physiologically based pharmacokinetic model for drug distribution and excretion is described. The physiological modeling procedure is useful in animal and clinical applications to obtain fundamental knowledge of the transport and metabolism of a substance *in vivo*. In this paper a review of physiologically based pharmacokinetics is presented in the hope of understanding and increasing the use of this modelling technique. The method of model development and the composition of equations based on the different models are explained. For the better understanding a physiological pharmacokinetic model of tenoxicam disposition in the rat is presented as an example of flow limited model.

1. BACKGROUND AND BENEFIT OF PHYSIOLOGICAL PHARMACOKINETIC MODEL

Physiological pharmacokinetic modeling attempts to utilize basic physiological and biochemical information to predict the time-dependent concentrations of a drug in a living system. Whereas classical approaches are usually based on the curve fitting of plasma concentration data with multiexponential equations to construct the necessary compartmental models. Although these conventional models are useful for drug treatment in many clinical situations[1] this modeling procedure can not describe a physiological system with large tissue-to-tissue concentration differences. This intercompartment variation is not tolerable especially for drugs that have high affinities for certain organs and that have specific target organs. For example, cardiac drugs like digitalis or ultrashort-acting barbiturates like thiopental, have rather narrow margins of safety and the distribution in blood does not provide sufficient information for adequate therapy. Digitalis kinetics in heart muscle and thiopental kinetics in brain can provide much better information for optimal therapy[2]. Physiological modeling allows the description of individual tissue concentrations and intercompartmental variation which is necessary to provide optimal treatment. The parameters obtained from classical pharmacokinetics contain little physiological basis and do not allow for scaling between species. Physiological parameters such as tissue volume, blood flow etc., are scalable from species to species. As the drug concentration in an individual organ is difficult to measure in humans and it may not be possible to investigate the pharmacokinetics of some highly toxic substances in humans, the ability to scale-up a model to the human based on experiments with smaller species, could lead to the safer use of drugs.[3-6]

Physiological pharmacokinetic model also allow the prediction of drug distribution and elimination when the drug is administered to patients or animals that are in altered or abnormal biochemical or physiological state[7,8].

For example, in the case of renal or liver insufficiency, the drug concentrations in plasma and individual organs can be predicted by reducing the renal or liver clearance in the model. Drug disposition in pregnancy can be also well estimated from small animal experiments through the use of physiological pharmacokinetic modeling.[5,9-11].

2. DEVELOPMENT OF A PHYSIOLOCICAL MODEL

For the development of a physiological pharmacokinetic model, the living system is separated into a number of anatomical compartments representing organs or tissue spaces whose drug concentrations are assumed to be uniform, and each compartment is inter-connected through the body fluid systems.

The kind of information required for model

development can be classified as

1. organ volumes and tissue sizes.
2. blood flow rates for individual organs and tissues.
3. transport mechanisms for drug across a biological membrane.
4. biliary and urinary excretion of drug.
5. metabolism, i.e., degradation or change of the drug in the body.
6. drug binding to plasma and tissue proteins.

Some of the information, like transport, metabolism, and drug binding may be ignored or expressed in simple terms for certain drugs or organs. Differential mass balance equations are written for each compartment to describe input, output, accumulation, or disappearance of drug. These equations are solved numerically, using specified parameters to simulate the drug concentration-tme data.[12-15]

There are two limiting cases for the model depending on the cell membrane permeability of the drug, a flow-limited or a membrane-limited model. The flow-limited model can be used for a drug which has a much larger cell membrane permeability than the blood flow. In this case, the rate of drug distribution into a tissue is limited by the rate of blood flow since the transmembrane transport is relatively rapid.[16-18]

The membrane-limited model presents the opposite case. When the cell membrane permeability is low compared to the blood perfusion rate, the rate of drug uptake by a tissue is limited by the rate of transfer across the cell membranes.[11,19,20]

The choice of model varies from drug to drug, and from tissue to tissue. Both flow-limited and membrane limited compartments can exist within the same overall model.[6,21]

2.1. Flow limited model

The flow limited assumption is made for organs not well perfused by the circulatory system. This assumption implies that the transfer across the capillary wall and across the cellular membrane is very rapid when compared with the perfusion rate of the tissue. This assumption of flow-limited transport is applicable to relatively low molecular weight, weakly ionized, lipid-soluble drugs for which diffusion across lipoidal membranes should be relatively rapid.[13,22]

In other words, the drug concentration in capillary blood, interstitial water, and intracellular space are in equilibrium when the model for blood perfusion of the local tissue region is expressed as in Figure 1.[13]

The mass balance equation for a noneliminating compartment is expressed as:

$$V_i \frac{dC_i}{dt} = Q_B i.\ R_B \left(C_B - \frac{C_i}{R_B i}\right) \tag{1}$$

where V_i, C_i and $Q_B i$ are the volume, drug concentration and blood flow rate to the organ or tissue, respectively. C_B is the drug concentration in blood and R_B is the whole blood to plasma concentration ratio. $R_B i$ is the partition coefficient, which is the ratio of the drug concentration in the tissue to the drug concentration in the blood at equilibrium. Under the assumption that the drug does not enter blood cells or that the equilibrium between drug concentration in blood cells and plasma is achieved very quickly[16] the equation can be simplified as:

$$V_i \frac{dC_i}{dt} = Q_i \left(C_P - \frac{C_i}{R_i}\right) \tag{2}$$

where Q_i is the plasma flow rate of organ or tissue, C_P is the drug concentration in plasma, and R_i is the partition coefficient of tissue and plasma drug concentration at equilibrium.

For eliminating organs the mass balance equation is written as:

$$V_i \frac{dC_i}{dt} = Q_i \left(C_P - \frac{C_i}{R_i}\right) - q_i \tag{3}$$

where q_i is the amount of drug excreted per unit time. This equation can be expressed by a first order approximation:

$$V_i \frac{dC_i}{dt} = Q_i \left(C_P - \frac{C_i}{R_i}\right) - K_i \cdot C_i \tag{4}$$

where k_i is the first order elimination rate constant. If the excretion or metabolism kinetics are saturable, and follow Michaelis-Menten kinetics, Equation (4) would become:

$$V_i \frac{dC_i}{dt} = Q_i \left(C_P - \frac{C_i}{R_i}\right) - \frac{C_i \cdot v_{max}}{K_m + C_i} \tag{5}$$

where v_{max} is the theoretical maximum rate of the process, and K_m is the Michaelis constant. The Michaelis constant should be determined by fitting the model to the excretion data[22]. A mass balance for the plasma compartment is made to close the balance on the system:

$$V_P \frac{dC_P}{dt} = \sum_i Q_i \frac{C_i}{R_i} - Q_P \cdot C_P \tag{6}$$

2.2. Membrane limited model

The membrane limited assumption is applicable when the drug transfer across the capillary or cell membrane is slow and close to the perfusion rate

for the tissue. The model can theoretically include one, two or three subcompartments according to the membrane limiting step (Figure 1).

2.2.1. *One subcompartment*

If the drug transport in membrane limited, and the drug concentration in capillary, interstitial and intracellular space are in equilibrium, the mass balance equation for the compartment is written:

$$V_i \frac{dC_i}{dt} = n^{P-T} \tag{7}$$

where n^{P-T} is the flux across the membrane from blood to the tissue compartment. The transport of a drug across the membrane may occur by passive diffusion, active transport, or by a combination of these processes[6,11]. For the case of passive diffusion, the flux across the membrane is described by a mass transfer coefficient (h_i):

$$n^{P-T} = h_i (C_P - \frac{C_i}{R_i}) \tag{8}$$

A mass balance for the plasma compartments is made by Equation (6).

2.2.2. *Two subcompartments.*

If the drug transfer is limited by the cell membrane in figure 1, there are two subcompartments, the intracellular space and the extracellular space. The intracellular space consists of the tissue cells, and the extracellular space consists of the capillary and interstitial subcompartments in equilibrium. A mass balance equation for the extracellular space is written as:

$$V^E \frac{dC^E}{dt} = Q_i (C_P - C^E) - n^{E-C} \tag{9}$$

where n^{E-C} is the flux across the cell membrane from extracellular space to cellular space. V^E and C^E are the volume and the drug concentration for the extracellular compartment of the organ or tissue. The accumulation in the cellualr space can be expressed as a net transfer to the cellular space.

$$V^C \frac{dC^C}{dt} = n^{E-C} \tag{10}$$

where V^C is the volume of cellular space. The drug concentration in the whole organ or tissue is volume averaged as:

$$C_i = \frac{V^E \cdot C^E + V^C \cdot C^C}{V_i} \tag{11}$$

For the plasma compartment, the mass balance equation is:

$$V_P \frac{dC_P}{dt} = \sum_i Q_i \cdot C_i^E - Q_P \cdot C_P \tag{12}$$

If the limitation to transfer of drug is across the capillary wall, then the transfer is assumed to be capillary membrane limited. In this case, the interstitial and cellular spaces are assumed to be in equilibrium. Therefore, the two subcompartments are the capillary space and cellular space (including interstitial space). For the capillary membrane limited model, equations similar to Equation (9)-(12) can be used.

2.2.3. *Three subcompartments*

To form a three subcompartment model, mass balance equations for the drug in capillary, interstitial, and cellular subcompartments of the organ or tissue are written, respectively, as:

$$V^V \frac{dC^V}{dt} = Q_i \cdot C_P - Q_i \cdot C^V - n^{V-I} \tag{13}$$

$$V^I \frac{dC^I}{dt} = n^{V-I} - n^{I-C} \tag{14}$$

$$V^C \frac{dC^C}{dt} = n^{I-C} \tag{15}$$

where V^V and C^V are the volume and the drug concentration for the capillary space of the organ or tissue. V,I, and C represent capillary space, interstitial space, and cellular space, respectively. The total compartment concentration is volume averaged as:

$$C_i \frac{C^V \cdot C^V + C^I \cdot V^I + C^C \cdot V^C}{V_i} \tag{16}$$

The mass balance equation for the plasma compartment is written as:

$$V_P \frac{dC_P}{dt} = \sum_i Q_i \cdot C_i^V - Q_P \cdot C_P \tag{17}$$

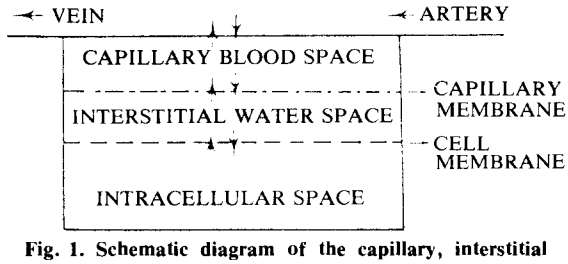

Fig. 1. Schematic diagram of the capillary, interstitial and intracellular spaces of an organ. The arrows represent the direction of drug transportation.

2.3. *Estimation of parameters used for the model development*

The physiological parameters such as blood flow rate (Q_B) and organ volume (V_i) can be measured by

experiment[20,23] or scaled based on physiological information.[3,19,21,24]

For most species, these values are readily found in the literature.[21,24] Partition coefficients (R) can be measured experimentally following long-term infusion[5] estimated from the data after an I.V. bolus injection[25,26] or from *in vitro* studies.[5,27] Elimination rate constants (k) can be calculated from excretion data.[18,28] If any separate experiments or appropriate literature values are not available to estimate a particular parameter value, it may be determined from the best fit of the simulation to the drug concentration-time data.[5,10,20]

For example, passive diffusion rate constants (h) can be estimated by solving the differential mass balance equations to match the experimental tissue drug concentrations during the distribution phase[6,29].

3. An Example: PHYSIOLOGICAL PHARMACOKINETIC MODEL FOR THE DISTRIBUTION AND ELIMINATION OF TENOXICAM

3.1. Physiological Model Development and Calculations

The physiological pharmacokinetic model utilized in this study is shown in Figure 2. The model was constructed on the basis of the following assumptions: (1) Each tissue is a well stirred compartment, (2) The drug distribution is flow limited except for the testes, and (3) Tissue to plasma partition coefficients are concentration and time independent. The carcass serves as a residual compartment, and includes tissues and organs not otherwise incorporated into the model. The model includes four drug clearances; metabolic, kidney, bile and faeces clearance. The blood flow to the liver was defined as the sum of flow from stomach, spleen, pancreas, intestine and direct flow from the hepatic artery. Gut absorption (K_{GI}) and excretion (K_{IG}) rate constants are included between the intestine and gut lumen. Drug distribution for testes was simulated as a membrane limited passive diffusion model.

The following mass-balance equations describe the drug concentration in each compartment of the physiological model.

Venous

$$V_{Ve}\frac{dC_{Ve}}{dt} = Q_r\frac{C_{Br}}{R_{Br}} + Q_{He}\frac{C_{He}}{R_{He}} + Q_{Li}\frac{C_{Li}}{R_{Li}} + Q_{Ki}\frac{C_{Ki}}{R_{Ki}} + Q_{Mu}\frac{C_{Mu}}{R_{Mu}} + Q_{Fa}\frac{C_{Fa}}{R_{Fa}} + Q_{Te}\frac{C_{Te}}{R_{Te}} + Q_{Sk}\frac{C_{Sk}}{R_{Sk}} + Q_{Bo}\frac{C_{Bo}}{R_{Bo}} + Q_{Ca}\frac{C_{Ca}}{R_{Ca}} - Q_{Ve}\cdot C_{Ve}$$

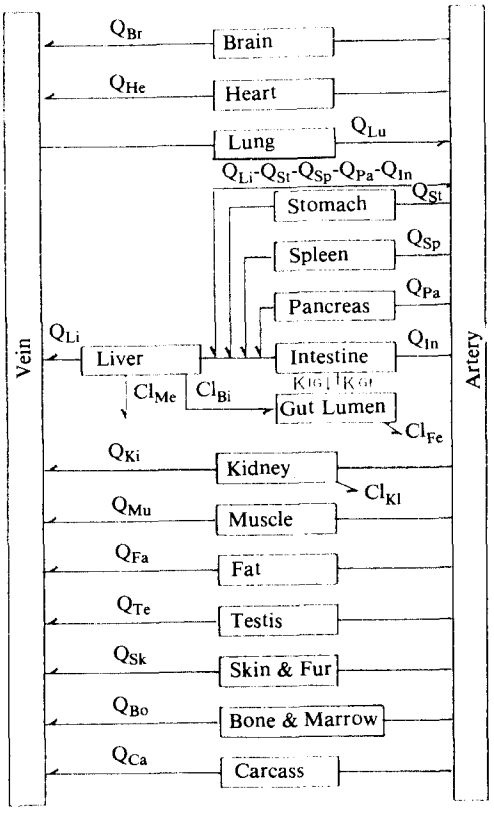

Fig. 2. Physiological pharmacokinetic model of tenoxicam disposition in the rat.

Artery

$$V_{Ar}\frac{dC_{Ar}}{dt} = Q_{Lu}\frac{C_{Lu}}{R_{Lu}} - Q_{Ar}\cdot C_{Ar}$$

Testes

$$V_{Te}\frac{dC_{Te}}{dt} = h_{Te}\left(C_{Ar} - \frac{C_{Te}}{R_{Te}}\right)$$

Lung

$$V_{Lu}\frac{dC_{Lu}}{dt} = Q_{Ve}\cdot C_{Ve} - Q_{Lu}\frac{C_{Lu}}{R_{Lu}}$$

Liver

$$V_{Li}\frac{dC_{Li}}{dt} = C_{Ar}(Q_{Li} - Q_{St} - Q_{Sp} - Q_{Pa} - Q_{In}) + Q_{St}\frac{C_{St}}{R_{St}} + Q_{Sp}\frac{C_{Sp}}{R_{Sp}} + Q_{Pa}\frac{C_{Pa}}{R_{Pa}} + Q_{In}\frac{C_{In}}{R_{In}} - Q_{Li}\frac{C_{Li}}{R_{Li}} - Cl_{Li}\cdot C_{Ar}$$

Kidney

$$V_{Ki}\frac{dC_{Ki}}{dt} = Q_{Ki}\left(C_{Ar} - \frac{C_{Ki}}{R_{Ki}}\right) - Cl_{Ki}\cdot C_{Ar}$$

Intestine

$$V_{In}\frac{dC_{In}}{dt} = Q_{In}(C_{Ar} - \frac{C_{In}}{R_{In}}) + K_{GI}\cdot V_{Gu}\cdot C_{Gu} - K_{IG}\cdot V_{In}\cdot C_{In}$$

Gut lumen

$$V_{Gu}\frac{dC_{Gu}}{dt} = Cl_{Bi}\cdot C_{Ar} + K_{IG}\cdot V_{In}\cdot C_{In} - K_{GI}\cdot V_{Gu}\cdot C_{Gu} - Cl_{Fe}\cdot C_{Gu}$$

Non eliminating organs; stomach, spleen, pancreas, muscle, fat, brain, skin and fur, bone and marrow, and carcass

$$V_i\frac{dC_i}{dt} = Q_i(C_{Ar} - \frac{C_i}{R_i})$$

Urine

$$\frac{dC_{Ur}}{dt} = Cl_{Ki}\cdot C_{Ar}.$$

where

V_i = tissue volume (m*l*)
C_i = drug concentration (ug/m*l*)
Q_i = plasma flow (m*l*/hr)
R_i = tissue to plasma partition coefficient
Cl_i = clearance in organ or tissue (m*l*/hr)
Cl_{Fe} = faeces clearance (m*l*/hr)
Cl_{Bi} = bile clearance (m*l*/hr)
h_{Te} = mass transfer coefficient (membrane diffusion parameter, m*l*/hr)
K_{GI} = first order rate constant for gut secretion (m*l*/hr)
K_{IG} = first order rate constant for gut absorption (m*l*/hr)

The subscripts are as follows: Ve, venous; Ar, artery; Br, brain; He, heart; Li, liver; Ki, kidney; Mu, muscle; Fa, fat; Te, testes; Sk, skin and fur; Bo, bone and marrow; Ca, carcass; Lu, lung; St, stomach; Pa, pancreas; In, intenstine; Gu, gut lumen; Bi, bile; Fe, faeces; Ur, urine; Me (Figure 2.) metabolic.

Table I. Physiological Parameters Used in the Model for 240 g Wistar Rat.

Organ	Volume[a] (V, m*l*)	Plasma flow rate(Q, m*l*/hr)	Linear binding constant[a] (R)	MDRC[b] * (h, m*l*/hr)	Clearance[c] (Cl, m*l*/hr)
Venous	7.0	1800[d]	0.014	—	—
Artery	3.5	1800[d]	—	—	—
Brain	1.54	27[e]	0.014	—	—
Heart	0.65	48[d]	0.18	—	—
Lung	0.98	1800[d]	0.31	—	—
Stomach	2.11	72[f]	0.14	—	—
Spleen	0.36	27[f]	0.07	—	—
Pancreas	0.52	32[f]	0.12	—	—
Intestine	8.4	420[f]	0.25	—	—
Gut lumen	4.5	—	—	—	—
Liver	5.24	686[f]	1.12	—	5.48
Kidney	1.38	438[d]	1.01	—	0.023
Muscle	108[d]	216[d]	0.08	—	—
Fat	16.8[e]	60[d]	0.03	—	—
Testes	2.88	22.6[f]	0.09	0.27	—
Skin & Fur	45.2[e]	144[d]	0.15	—	—
Bone[h]	14.8[e]	76.8[g]	0.10	—	—
Carcass	16.1[c]	81.6[c]	0.09[c]	—	—
Bile clearance (Cl_{Bi})					0.52
Faeces clearance (Cl_{Fe})					1.20
Gut absorption and excretion rate constant (K_{IG}, K_{GI})					0.05[b]

a) experimental data. b) estimated from experimental data. c) calculated from data. d) Ref. 21 e) Ref. 13 f) Ref. 11 g) Ref. 16 h) bond and marrow. *Membrane diffusion rate constant

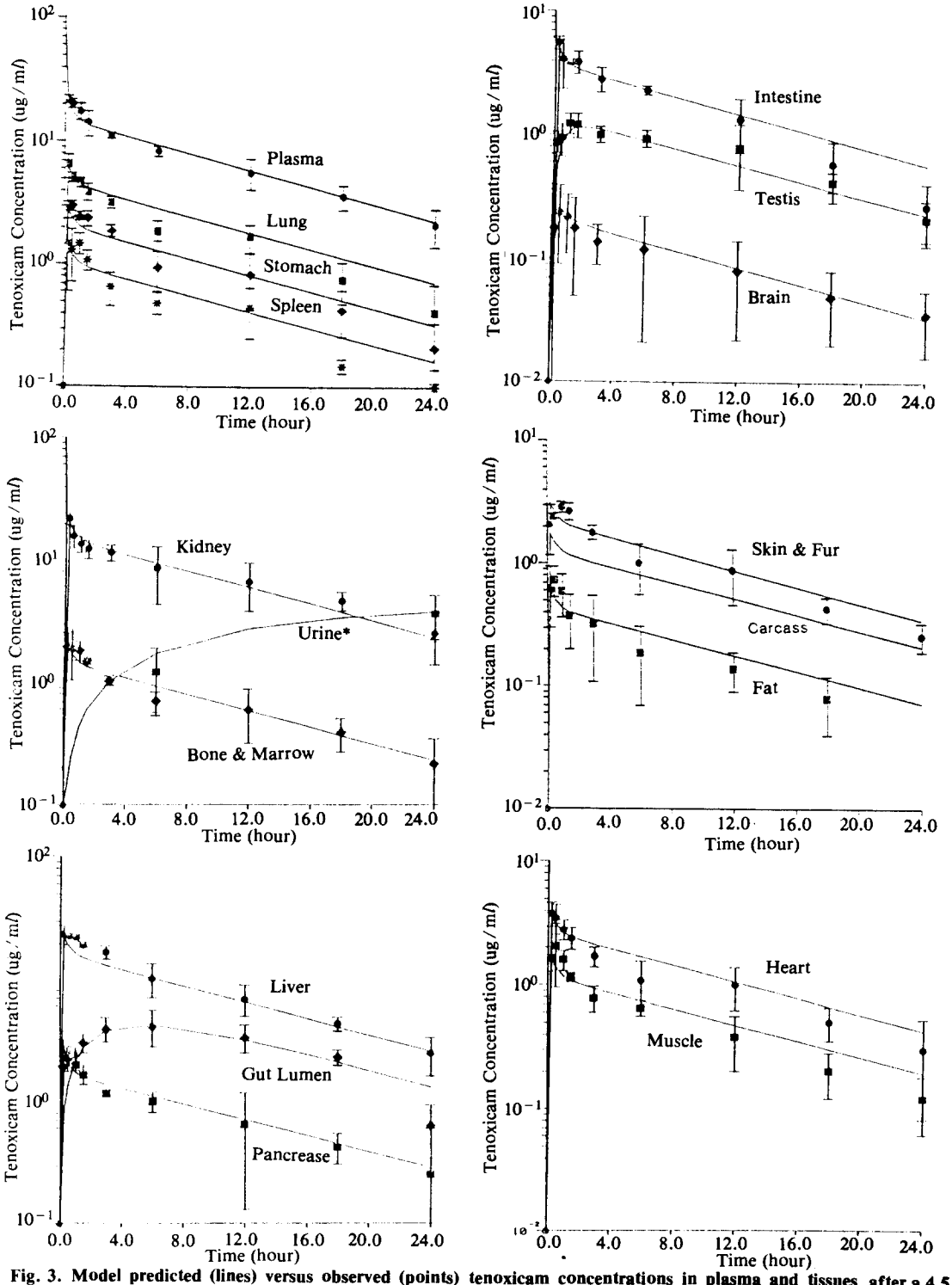

Fig. 3. Model predicted (lines) versus observed (points) tenoxicam concentrations in plasma and tissues after a 4.5 mg/kg intravenous bolus dose to rats. Each point and bar represents a mean of 5 experimental data and a standard deviation respectively. *Cumulative amount (ug) of tenoxicam excreted in the urine.

The nineteen differential equations of the model were solved simultaneously using the program MULTI-FORTE[30,31] on a Macintosh 512K desktop computer

3.2. Determination of Model Parameters

The physiological parameters used in the model are summarized in Table 1. The partition coefficients (R value) and the volume of the most of the organs were determined experimentally as a mean of 5 measurements. The volume of plasma, muscle, fat, skin and fur, bone and marrow were taken from the literature values[13,21] with an assumed tissue density of 1/m*l*. Plasma flow rates were also taken from literature[11,13,16,21] and scaled to a body weight of 240 g when necessary. The R value of carcass was calculated as a volume proportional mean of the non-eliminating organs, and the volume of carcass was calculated by substracting the sum of all other tissues and plasma from the total rat weight of 240 g. The plasma flow rate of carcass was calculated as the difference between venous flow rate and sum of output tissue plasma flow rate to venous. The diffusion parameters into testes (h_{Te}), gut absorption (K_{GI}) and excretion (K_{IG}) rate constants were adjusted to obtain a reasonable simulation of the data. The total body clearance and renal clearance (Cl_{Ki}) values were calculated from the data as Dose/AUC and $k_u \times V_1$ respectively, where AUC is the area under the plasma drug concentration versus time curve. k_u is the excretion rate constant into urine, and V_1 is the volume of distribution of the central compartment for a two compartment pharmacokinetic model. The hepatic clearance term (Cl_{Li}) was calculated as the difference between the total clearance and the renal clearance values. The bile clearance (Cl_{Bi}) was estimated from the amount of drug in the gut lumen, and the faeces clearance (Cl_{Fe}) was estimated from the amount of drug excreted into faeces.

3.3 Validation of the Physiological Model

The physiological model developed herein simulates the disposition and elimination of tenoxicam in plasma, urine, faeces, gut lumen and fifteen other tissue compartments of the male rat. The model was used to obtain the solid lines shown in Figure 3 with the experimental results represented by the symbols and error bars (mean ± SD). Good correlations were obtained over the 24 hr simulation period for 15 tissues and plasma. The great majority of drug concentrations in tissues and plasma were simulated within 20% of the experimental determinations except for some scattered data points. The model also simulates the sum of urine excretion and gut lumen contents within about 10% and 15% of the experimental determinations, respectively. Brain, testes, and spleen were initially calculated using membrane limited passive diffusion equations because of the delay in the peak time for these well perfused tissues. However, the 'best fit' values for the membrane perfusion coefficients were not different from the plasma flow rates to the brain or spleen. Thus, only the testes were calculated with a membrane limited passive diffusion equation. With a fitted value for the mass transfer coefficient there is good agreement between the model generated and the experimental data.

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