Table III—Effect of 4,4′-Diisothiocyano-2,2′-disulfonate Stilbene (II) and Calcium Chloride (III) on the Enhancement of Plasma Cefoxitin Levels and on Cefoxitin Disappearance from the Rat Rectal *In Situ* Loop by α-Glycerophosphate (I), Sodium Tripolyphosphate, and Sodium Phytate [a]

Adjuvant Concentration	Additive Concentration	Percent Disappearance of Cefoxitin at 1.5 h	$[AUC]_{0-30}$, μM·min
None	None	5.4 ± 5.8	<13 [b]
I (205 mM)	None	38.7 ± 8.1	119 ± 28
	II (1 mg/mL)	16.8 ± 6.3 [b]	52 ± 11 [b]
	III (180 mM)	25.2 ± 5.3	99 ± 18
Tripolyphosphate (108 mM)	None	18.5 ± 4.2	61 ± 11
	II (1 mg/mL)	21.9 ± 7.1	66 ± 9
	III (180 mM)	7.8 ± 3.2 [b]	<13 [b]
Phytate (53 mM)	None	21.8 ± 5.1	67 ± 8
	II (1 mg/mL)	22.5 ± 5.4	77 ± 12
	III (180 mM)	7.6 + 3.9 [b]	<13 [b]

[a] Microenemas contained 15 mg of cefoxitin/mL and had a dosage volume of 100 μL/100 g of rat body weight; $n \geq 3$. [b] $p < 0.001$ *versus* adjuvant without additive.

difference in their ability to permeate the rat rectal tissue. In the present study, we found that the coadjuvants tripolyphosphate and phytate substantially enhanced the absorption of cefoxitin only after their own permeation of the membrane was apparently enhanced by I. Thus, we speculate that adjuvant permeation of the mucosal membrane may be mechanistically necessary before enhanced compound absorption across the rectal membrane can occur.

In conclusion, the enhancing action of I on rectal cefoxitin absorption appears to depend on the affinity of I to the protein fraction in the mucosal membrane. The weak enhancing ability of the phosphate coadjuvants when administered with cefoxitin alone may involve chelating activity and possible damage to the rectal mucosa. However, the large increase in drug absorption after coadministration of I with either chelating agent, tripolyphosphate or phytate, is not just a consequence of the added effect of the enhancing action of I and chelation. These phosphate derivatives apparently have a strong adjuvant efficacy which can be realized only when their own permeation of the mucosal membrane is enhanced by adjuvants such as I.

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Physiological Model for Distribution of Sulfathiazole in Swine

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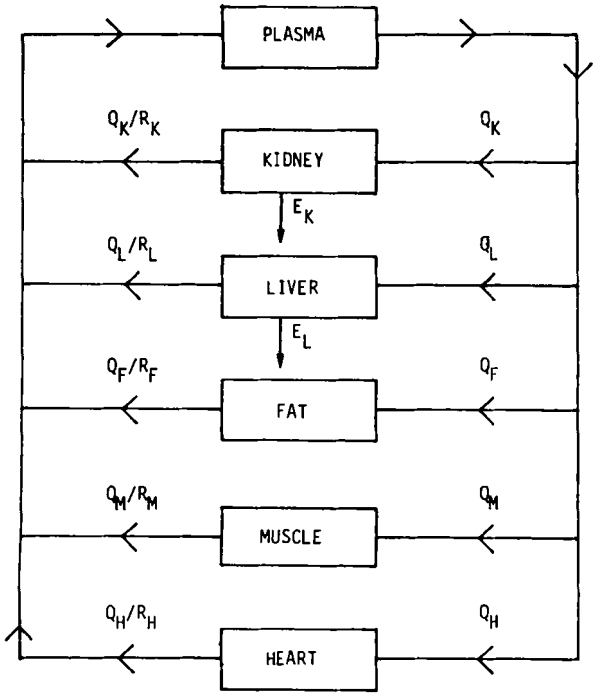
Received August 29, 1983, from the * *College of Pharmacy and the* ‡ *Department of Mathematics, University of Kentucky, Lexington, KY 40506.* Accepted for publication December 19, 1983. Present addresses: §Department of Mathematics, De Paul University, Chicago, IL 60614 and ¶ Department of Pharmacy, University of Queensland, St. Lucia, 4067, Australia.

Abstract □ A physiological flow model was developed for the distribution of sulfathiazole residues in various tissues in swine. The approach was compartmental, in which the compartments and equilibrium constants had physiological meaning. Differential equations were developed, and appropriate parameter values and initial conditions were substituted and solved by a fourth-order Runga-Kutta technique. Simulation values corresponded with the experimentally determined concentration values in plasma and kidney, liver, muscle, fat, and heart tissues.

Keyphrases □ Sulfathiazole—physiological flow model, distribution, swine □ Physiological flow model—sulfathiazole, swine, distribution □ Distribution—physiological model, sulfathiazole, swine

Allergic reaction and increasing bacterial resistance are possible side effects resulting from human consumption of meat derived from animals given antibiotics (1). Consequently, regulations have been promulgated by the Food and Drug Administration setting tolerance levels for antibiotics and other drugs in slaughtered animals (2). Mathematical models which predict the residual amounts of a given drug in various organs at various times after administration are therefore important



Scheme I—Body compartments in sulfathiazole distribution

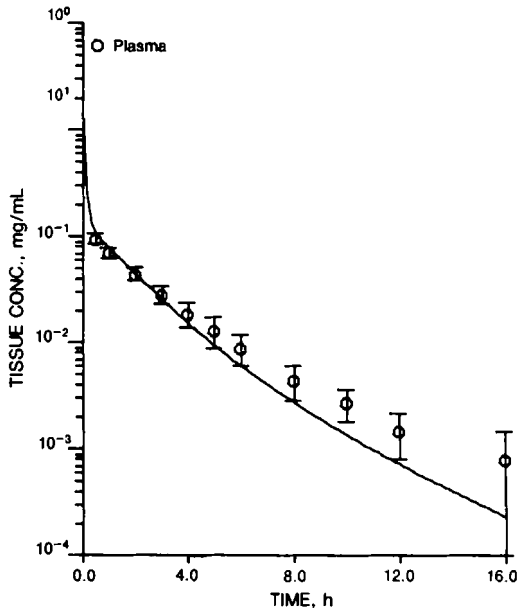


Figure 1—*Semilogarithmic plot of plasma concentration of sulfathiazole (O) versus time after intravenous administration to swine. The points were experimentally determined (SD as error bars), and the line was calculated according to Scheme I with the parameter values from Table I.*

in setting the minimum time until slaughter after administration of the drug. The model must be sensitive to a number of factors, including the characteristic properties of the drug, the species of the animals, and the weight of the animal.

In this report, a model developed for the distribution of sulfathiazole residues in a number of organs in swine is described. Previously, a two-compartment model was used to describe these data (3). This work has been extended by development of a physiologically based model. The additional information obtained and the accuracy of physiological models for drug tissue concentrations has been well recognized in human pharmacokinetic modeling, especially with chemotherapeutic agents. In general, data from a number of organs and knowledge of several physiological parameters are needed. This allows the more detailed physiological model to yield more information than the usual compartmental model, in which the parameters are not directly related to the physiology of the animal. The model developed in this report closely follows the basic ideas developed previously (4, 5) (the Bischoff-Dedrick model). This approach has been applied to pharmacokinetic models in humans for thiopental (5, 6), methotrexate (4, 7, 8), cytarabine (9), and salicylate (10).

Table I—Parameters for Sulfathiazole Distribution in Swine (34 kg)

Plasma Flow to Organs (Q), mL/min	
Q_m	280
Q_f	10
Q_l	460
Q_k	330
Q_h	97
Organ Volumes (V), mL	
V_m	18300
V_f	9610
V_l	790
V_k	165
V_h	200
V_p	1610
Tissue-to-Plasma Equilibrium Constant (R)	
R_m	0.4
R_f	0.2
R_l	1.0
R_k	3.0
R_h	0.55
Tissue Clearance (E), mL/min	
E_k	61.8
E_l	76.8

EXPERIMENTAL SECTION

Theoretical Basis—Like the Bischoff-Dedrick model, the approach described here is a compartmental approach in which the compartments and equilibrium constants have physiological meaning. Scheme I displays the pattern of blood flow through the animal. Since the drug is administered by rapid injection, it was assumed that at the initial time $t = 0$ h the total dose of the drug was homogeneously distributed throughout the plasma compartment.

Compartments corresponding to plasma, kidney, liver, muscle, fat, and heart have been included. Data were available for all of these tissues. In particular,

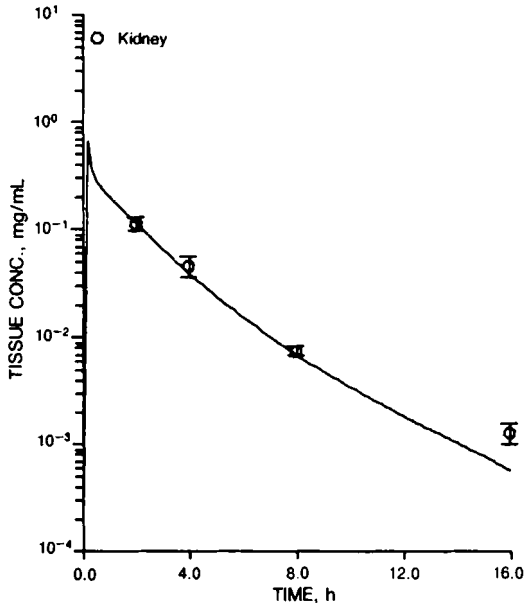


Figure 2—*Semilogarithmic plot of kidney concentration of sulfathiazole (O) versus time after intravenous administration to swine. The points were experimentally determined (SD as error bars), and the line was calculated according to Scheme I with the parameter values from Table I.*

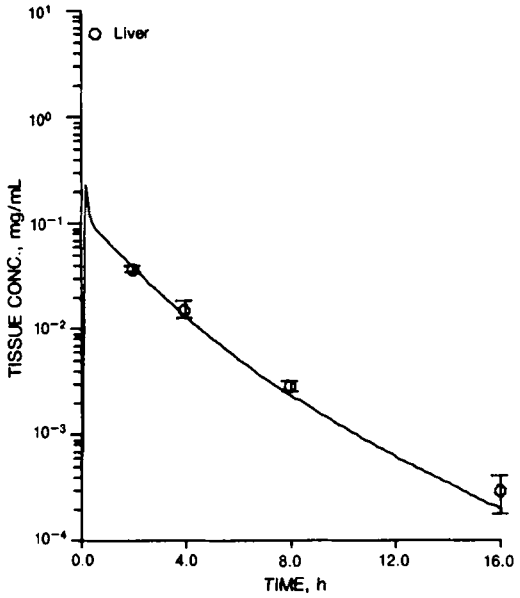


Figure 3—*Semilogarithmic plot of liver concentration of sulfathiazole (O) versus time after intravenous administration to swine. The points were experimentally determined (SD as error bars), and the line was calculated according to Scheme I with the parameter values from Table I.*

small amounts of drug were located in the heart, but it was included in the model as additional verification of the accuracy of the simulation.

From Scheme I a system of ordinary differential equations was derived by using the mass balance approach developed for physiological models (4, 5):

$$Vp \cdot \frac{dC_p}{dt} = \frac{Q_k}{R_k} \cdot C_k + \frac{Q_l}{R_l} \cdot C_l + \frac{Q_f}{R_f} \cdot C_f + \frac{Q_m}{R_m} \cdot C_m + \frac{Q_h}{R_h} \cdot C_h - (Q_k + Q_l + Q_f + Q_m + Q_h) \cdot C_p \quad \text{(Eq. 1)}$$

$$V_k \cdot \frac{dC_k}{dt} = Q_k \cdot C_p - \frac{Q_k}{R_k} \cdot C_k - \frac{E_k}{R_k} \cdot C_k \quad \text{(Eq. 2)}$$

$$V_l \cdot \frac{dC_l}{dt} = Q_l \cdot C_p - \frac{Q_l}{R_l} \cdot C_l - \frac{E_l}{R_l} \cdot C_l \quad \text{(Eq. 3)}$$

$$V_f \cdot \frac{dC_f}{dt} = Q_f \cdot C_p - \frac{Q_f}{R_f} \cdot C_f \quad \text{(Eq. 4)}$$

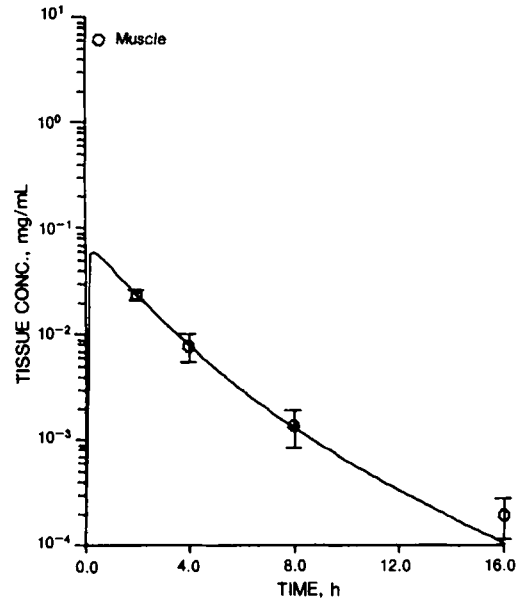


Figure 4—*Semilogarithmic plot of muscle concentration of sulfathiazole (O) versus time after intravenous administration to swine. The points were experimentally determined (SD as error bars), and the line was calculated according to Scheme I with the parameter values from Table I.*

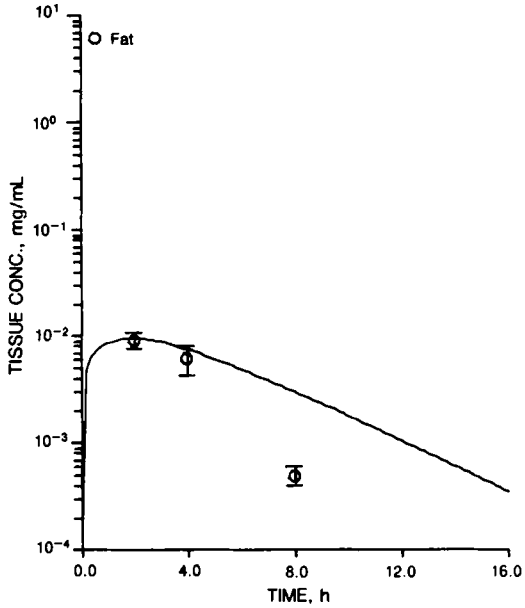


Figure 5—*Semilogarithmic plot of fat concentration of sulfathiazole (O) versus time after intravenous administration to swine. The points were experimentally determined (SD as error bars), and the line was calculated according to Scheme I with the parameter values from Table I.*

$$V_m \cdot \frac{dC_m}{dt} = Q_m \cdot C_p - \frac{Q_m}{R_m} \cdot C_m \quad \text{(Eq. 5)}$$

$$V_h \cdot \frac{dC_h}{dt} = Q_h \cdot C_p - \frac{Q_h}{R_h} \cdot C_h \quad \text{(Eq. 6)}$$

where V is volume, C is concentration, t is time, Q is plasma flow rate, R is the tissue to plasma equilibrium constant, E is the plasma clearance of the organ, and the subscripts represent the various organs: p for plasma, k for kidney, l for liver, f for fat, m for muscle, and h for heart. Hence, Q_m represents the plasma flow rate to the muscle.

The dose of the drug (D) was administered by rapid injection. By assuming it is instantly distributed through the plasma, the following initial conditions apply:

$$C_p(0) = D/V_p \quad \text{(Eq. 7)}$$

$$C_k(0) = C_l(0) = C_f(0) = C_m(0) = C_h(0) = 0 \quad \text{(Eq. 8)}$$

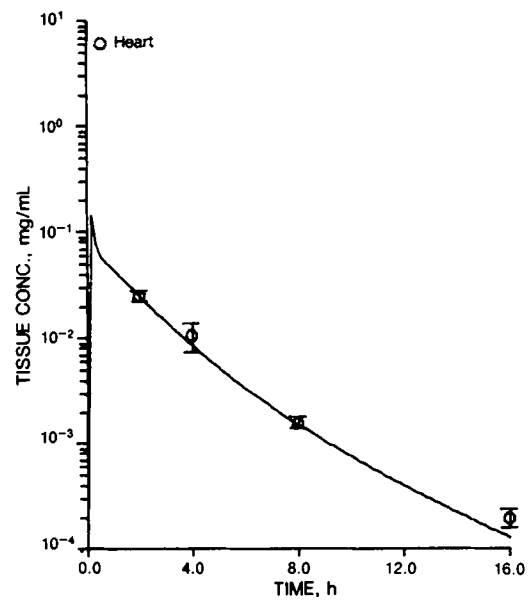


Figure 6—*Semilogarithmic plot of heart concentration of sulfathiazole (O) versus time after intravenous administration to swine. The points were experimentally determined (SD as error bars), and the line was calculated according to Scheme I with the parameter values from Table I.*

On substitution of appropriate parameter values and the initial conditions of Eqs. 7 and 8, Eqs. 1–6 were solved numerically by the fourth-order Runga-Kutta technique.

Parameters—Table I gives the parameters used in the simulation. The volumes for the blood, liver, kidney, and heart were obtained by first computing the organ weight by the method of Adolf (11) and then assuming a tissue density of 1 g/mL. Muscle and fat volumes were calculated from the percentages of body weight found in swine (12) and converted to the corresponding weight in the swine used. The average weight of the experimental swine was 34 kg. The plasma volume was computed as 60% of the whole blood volume. Bischoff *et al.* (13) have indicated that the method of Adolf of calculating blood volume produced a value lower than that reported in humans. Bischoff *et al.* have corrected for this difference by adjusting the Adolf values upward by a factor of 1.43. This adjustment was also made in this study.

Plasma flow rates for kidney, liver, and muscle were obtained from the relationship between plasma flow and body weight reported by Bischoff *et al.* (13). As fat is poorly perfused, it was assumed to have a very low flow rate. The actual value used was determined by perturbation. The heart plasma flow rate (adjusted for weight) was assumed to be the same as that for humans (14).

The total body clearance and renal clearance values were calculated from the data of Bourne *et al.* (3) as $k_{el} \cdot Vd$ and $k_e \cdot Vd$ respectively, where k_{el} is the elimination rate constant, k_e is the excretion into urine rate constant, and Vd is the apparent volume of distribution for a one-compartment pharmacokinetic model. The hepatic clearance term was calculated as the difference between the total body clearance and renal clearance values and represents the formation of an acetyl metabolite and sulfathiazole not recovered in urine.

The initial values for the equilibrium constants (R) were obtained from human autopsy (15) and were perturbed to obtain the simulation values. The dose of sodium sulfathiazole given to each animal was 72 mg/kg of body weight. In the simulation, the dose used was 2290.5 mg/kg of body weight, which was the average amount of sulfathiazole administered.

Experimental Data—The experimental data from Bourne *et al.* (3) were obtained by averaging the concentration of drug in the tissue of the three swine sacrificed at each time point. Sulfathiazole was extracted from tissues, as described by Bevill *et al.* (16), and quantitated by a modified Bratton-Marshall colorimetric method (17). The plasma concentrations (Fig. 1) were calculated as the average of the values obtained from the remaining swine at each time point. Plasma concentrations of sulfathiazole were measured by the modified Bratton-Marshall method of Annino (18).

RESULTS

The experimental data and the simulation for the plasma, kidney, liver, muscle, fat, and heart are shown in Figs. 1–6. The simulation parameters were chosen so that the graphs closely followed the trends indicated by the data. The values of those parameters which were obtained by experimentation or from the literature were not adjusted. The simulation results show a good correlation with the experimental data in all tissues except, possibly, fat. Data were collected from the muscle of the shoulder, loin, and leg. In Fig. 4, the experimental data are the average of these three concentrations in muscle tissue. The results obtained for fat tissue are shown in Fig. 5 (the simulation corresponds with the first two points, whereas the third point may indicate a factor not accountable by the model). The fat tissue included in the simulation is probably more diffuse than the samples taken for the experimental values.

DISCUSSION

A general physiological model has been presented for sulfathiazole in swine. The physiological meaning of each compartment allows the prediction of drug concentrations in those organs. The ability of the model to predict residue levels with reasonable accuracy in many different compartments suggests that the physiological approach is valuable. With this more complete model it should be possible to extrapolate or interpolate tissue concentrations of sulfathiazole in the various important food-providing tissues down to the regulated tolerance levels with more confidence than is possible with the linear compartmental approach. Given suitable estimates of the required parameters, drugs which are likely to give significant residue problems may be identified. Greater reliance on the model can be achieved with parameters specific for the species rather than parameters determined by extrapolation from other species.

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