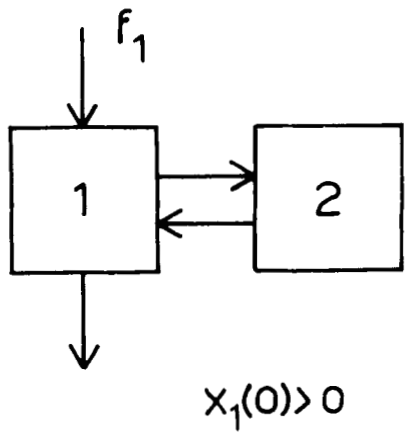

Scheme VI—Two-compartmental linear pharmacokinetic model used to demonstrate the partial transformation approach that does not require Laplace transformation of the input function f_1.

where, according to Eq. 21:

$$\Phi_{11}(t) = \frac{\alpha - E_2}{\alpha - \beta} e^{-\alpha t} + \frac{E_2 - \beta}{\alpha - \beta} e^{-\beta t} \quad \text{(Eq. 44)}$$

$$\Phi_{12}(t) = \frac{-k_{21}}{\alpha - \beta} e^{-\alpha t} + \frac{k_{21}}{\alpha - \beta} e^{-\beta t} \quad \text{(Eq. 45)}$$

$$\Phi_{21}(t) = \frac{-k_{12}}{\alpha - \beta} e^{-\alpha t} + \frac{k_{12}}{\alpha - \beta} e^{-\beta t} \quad \text{(Eq. 46)}$$

and $\alpha\beta = E_1E_2 - k_{12}k_{21}$ and $\alpha + \beta = E_1 + E_2$.

Equation 43 becomes, after substitution:

$$x_1 = \frac{\alpha - E_2}{\alpha - \beta} e^{-\alpha t} \left[x_1(0) + \int_0^t e^{\alpha t} f_1(t)\, dt \right] + \frac{E_2 - \beta}{\alpha - \beta} e^{-\beta t} \left[x_1(0) + \int_0^t e^{\beta t} f_1(t)\, dt \right] \quad \text{(Eq. 47)}$$

As an example, input f_1 may be in the form of a dissolution rate-limited release from an injected depot of slightly soluble crystalline drug. If it is assumed that *in vivo* dissolution follows the Hixson–Crowell relationship (13), then the input function may be written:

$$f_1(t) = -\frac{d}{dt} m_0(1 - k_d t)^3 = 3k_d m_0(1 - k_d t)^2 \qquad t < 1/k_d \quad \text{(Eq. 48)}$$

where m_0 is the dose injected and k_d is the *in vivo* dissolution constant. Substitution of this equation into Eq. 47 yields, after integration:

$$x_1 = \frac{3k_d m_0(\alpha - E_2)}{\alpha(\alpha - \beta)} \left[k_d{}^2 t^2 - \frac{2k_d{}^2 + 2\alpha k_d}{\alpha} t + \frac{2k_d{}^2 + 2\alpha k_d + \alpha^2}{\alpha^2} \right] + \frac{3k_d m_0(E_2 - \beta)}{\beta(\alpha - \beta)} \left[k_d{}^2 t^2 - \frac{2k_d{}^2 + 2\beta k_d}{\beta} t + \frac{2k_d{}^2 + 2\beta k_d + \beta^2}{\beta^2} \right] + \frac{\alpha - E_2}{\alpha - \beta} \left[x_1(0) - \frac{3k_d m_0(2k_d{}^2 + 2\alpha k_d + \alpha^2)}{\alpha^3} \right] e^{-\alpha t} + \frac{E_2 - \beta}{\alpha - \beta} \times \left[x_1(0) - \frac{3k_d m_0(2k_d{}^2 + 2\beta k_d + \beta^2)}{\beta^3} \right] e^{-\beta t} \qquad t < 1/k_d \quad \text{(Eq. 49)}$$

Equation 49 could have been obtained using a full transformation approach but that would require a somewhat larger derivation. The advantage of using a partial transform approach becomes particularly significant for more complex input functions.

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Physiological Perfusion Model for Cephalosporin Antibiotics I: Model Selection Based on Blood Drug Concentrations

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Received December 2, 1976, from the *School of Pharmacy, University of Connecticut, Storrs, CT 06268,* and the *Department of Medicine, Hartford Hospital, Hartford, CT 06115.* Accepted for publication May 2, 1977. *Present address: College of Pharmacy, University of Rhode Island, Kingston, RI 02881. ‡Present address: School of Pharmacy, State University of New York at Buffalo, Amherst, NY 14260.

Abstract □ Various cephalosporins with different degrees of protein binding were administered to human volunteers. Blood samples were collected as a function of time and were assayed for drug content by a microbiological assay. A pharmacokinetic analysis of the data was performed using a two-compartment model with and without protein binding in the central compartment and a perfusion model. Both the two-compartment model without protein binding and the physiological perfusion model adequately described the blood levels of all three cephalosporins.

Keyphrases □ Cephalosporins, various—pharmacokinetic analysis using two-compartment and perfusion models □ Antibiotics, various cephalosporin—pharmacokinetic analysis using two-compartment and perfusion models □ Models, pharmacokinetic—two-compartment and perfusion, for various cephalosporins

Compartmental models are a "black box" approach to predicting blood levels. The model consists of a central compartment, usually considered to be the plasma compartment, and possibly one or more tissue compartments. The compartments and the associated volumes and rate constants have no physiological meaning; *i.e.*, the plasma

Table I—Plasma Flows and Organ Weights for Perfusion Model Calculations

Tissue	Total Volume, liters	Extracellular[a] Volume, liters	Plasma[b] Flow, liters/hr
Bone	3.60[c]	—[d]	6.48[c]
Skin	3.00[c]	0.45	7.60[c]
RET	0.60[c]	0.09	57.60[e]
Muscle	33.00[e]	4.95	43.20[e]
Liver	3.90[e]	0.59	54.00
Blood	5.40[c]	3.24[b]	168.88[f]

[a] Calculated by multiplying total volume by 0.15, the fraction of tissue weight that is extracellular water (18). [b] Calculated by multiplying blood flow or blood volume by (1 − hematocrit), using an hematocrit of 0.40 (18). [c] From W. W. Mapleson, *J. Appl. Physiol.*, 18, 197 (1963). [d] Extracellular water not assumed for bone compartment. [e] Reference 9. [f] Calculated as sum of all plasma flows to listed tissues.

compartment does not consist of solely the plasma but also contains all well-perfused tissues. The number of compartments and the tissues in each compartment vary with different drugs, depending on the physical characteristics and binding of the drug. There are cases, however, where a physiological interpretation of parameters or compartments may be applicable (1).

Although the physiological interpretation of parameters obtained from compartmental analysis is limited, these models are useful for the prediction of blood levels and for the development of dosage regimens (1). The compartment models, however, have a very limited ability for predicting tissue levels.

The compartmental model approach does not address directly the serum protein binding of drugs. Although the shape and height of a serum level *versus* time curve are altered by protein binding and the resultant pharmacokinetic constants obtained from compartmental analysis reflects this change, specific information regarding the binding processes is usually not available.

A physiological perfusion model was proposed (2) to describe the uptake of thiopental by various tissues of the body. The model was revolutionary because it used physiological volumes and blood flows instead of black box compartments. The perfusion model was used to describe the pharmacokinetics of methotrexate (3–5) and cytarabine (6, 7). Other studies using the perfusion model also have appeared (8–10). The predictions that have been made of tissue and plasma levels have generally agreed well with experimental data.

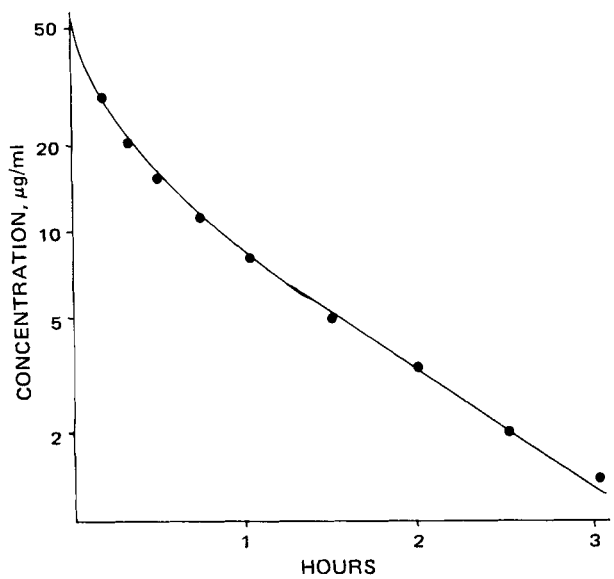


Figure 1—*Serum cephalexin concentration* versus *time after a 1-g iv dose.*

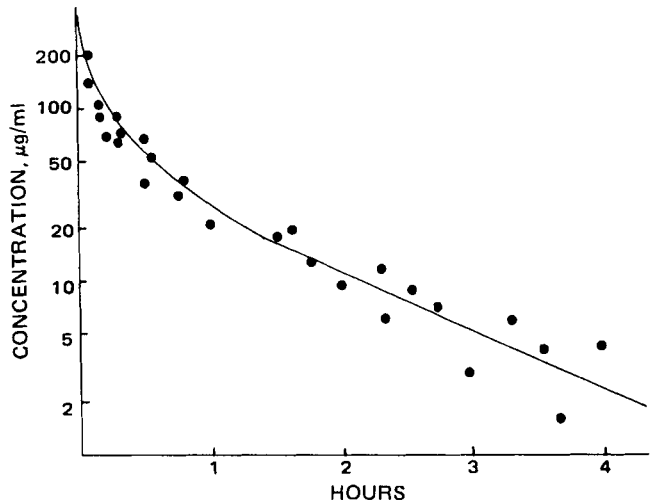


Figure 2—*Serum cephradine concentration* versus *time after a 2-g iv dose.*

The pharmacokinetics of the cephalosporins previously were studied using a compartmental analysis (11–14). Physiological blood flow models have not been investigated for these drugs. The purpose of this study was to evaluate the pharmacokinetics of cefazolin (highly bound) and cephradine and cephalexin (negligibly bound) using a variety of models to describe the data.

EXPERIMENTAL

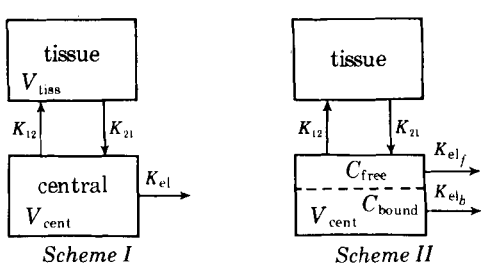
The cephalosporins selected for study, *i.e.*, cefazolin, cephalexin, and cephradine, were reported to be 88, 10, and 15% bound to human plasma proteins at normal therapeutic concentrations, respectively. One gram of cefazolin, 0.5 g of cephalexin, and 2.0 g of cephradine were administered intravenously to five healthy human volunteers. Blood samples were collected as a function of time for 4 hr after administration.

Several weeks lapsed between the administration of each drug. Serum was separated from blood and frozen until assayed, using a disk diffusion microbiological technique (15).

PHARMACOKINETIC MODELING

Three models were used to fit the data: a two-compartment model, a two-compartment model with protein binding, and a perfusion model. The two-compartment model without protein binding (Scheme I) was modified by the addition of binding within the central (plasma) compartment (Scheme II). The following assumptions were made in the development of the model:

1. Binding is present only in the central compartment; all drug in the tissue compartment is in the free form.
2. Distribution and elimination are linear processes.
3. Only free drug is able to distribute to the tissue compartment; *i.e.*, the rate of distribution is proportional to the free drug concentration.
4. The binding equilibrium in the central compartment occurs in-



Scheme I *Scheme II*

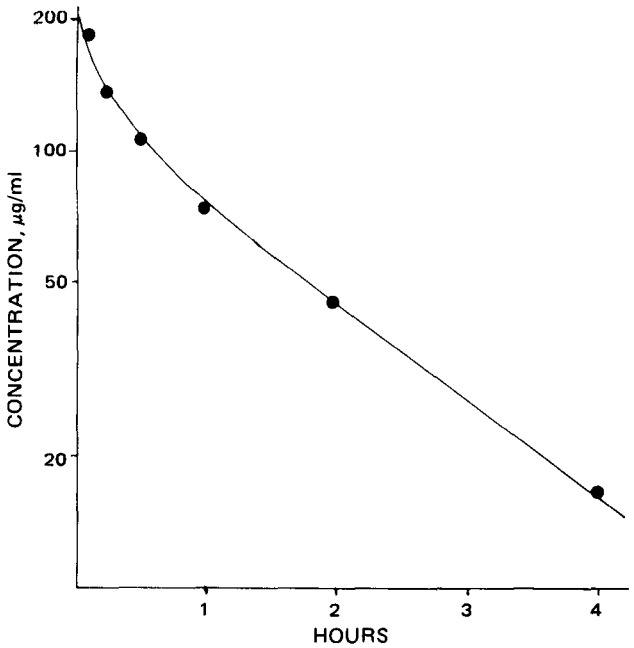


Figure 3—*Serum cefazolin concentration* versus *time after a 1-g iv dose.*

stantaneously, the concentrations of free and bound drugs being defined by:

$$C_B = \frac{n_1 K_{a_1} P C_f}{1 + K_{a_1} C_f} + \frac{n_2 K_{a_2} P C_f}{1 + K_{a_2} C_f} \qquad \text{(Eq. 1)}$$

where C_B and C_f represent the bound and free concentrations of drug, respectively; n_1 and n_2 and K_{a_1} and K_{a_2} represent the numbers of binding sites and affinity constants, respectively, for each type of binding site; and P represents the concentration of protein in the central compartment.

The concentration of protein is assumed to be constant throughout the central compartment. It is expected that the fitted volume of the central compartment approaches the plasma volume (3.2 liters).

5. Elimination of both free and bound drug occurs. The rate constant for the elimination of the drug is a sum of the elimination rate constants of free and bound drug.

The differential equations used to fit the serum concentrations of cefazolin were:

$$\frac{d(C_t)}{dt} = K_{21} C_2 - K_{12} C_f - K_{el_b} C_b - K_{el_f} C_f \qquad \text{(Eq. 2)}$$

$$\frac{d(C_2)}{dt} = K_{12} C_f - K_{21} C_2 \qquad \text{(Eq. 3)}$$

where C_2 represents the concentration of drug in the tissue compartment, and C_f and C_t represent the free and total concentrations of drug in the central compartment, respectively. The rate constants K_{12}, K_{21}, K_{el_b}, and K_{el_f} are defined in Scheme II.

All data were fit using an overall rate constant, K_{el}, which represented the sum of K_{el_b} and K_{el_f}. All serum level data were in the form of the total concentration of cefazolin in the plasma. The free concentration of cefazolin in the plasma was calculated by solving Eq. 1 for C_f. The initial conditions for the integration of these equations were C_t = dose/V_c and $C_2 = 0$ at time = 0 for Eqs. 2 and 3, respectively, where V_c represents the volume of the central compartment.

A perfusion model similar to that by Benowitz *et al.* (9) was developed for the cephalosporin antibiotics using the following assumptions:

1. The equilibrium between free and bound drug is an instantaneous process, the free and bound drug concentrations being described by the Scatchard equation (Eq. 1).

2. Only free drug is able to leave the plasma and enter the tissue; the bound drug is retained in the plasma.

3. The distribution of drug between the plasma and tissues is blood flow limited.

4. Drug does not enter the cells of the tissues; all drug is contained within the extracellular water of the tissues.

5. Drug in the blood is restricted to the plasma water; the drug is unable to enter the erythrocytes.

6. Elimination of drug occurs by: (*a*) glomerular filtration—only the free drug is filtered in the glomerulus, and (*b*) tubular secretion—both free and bound drug are removed by active secretion.

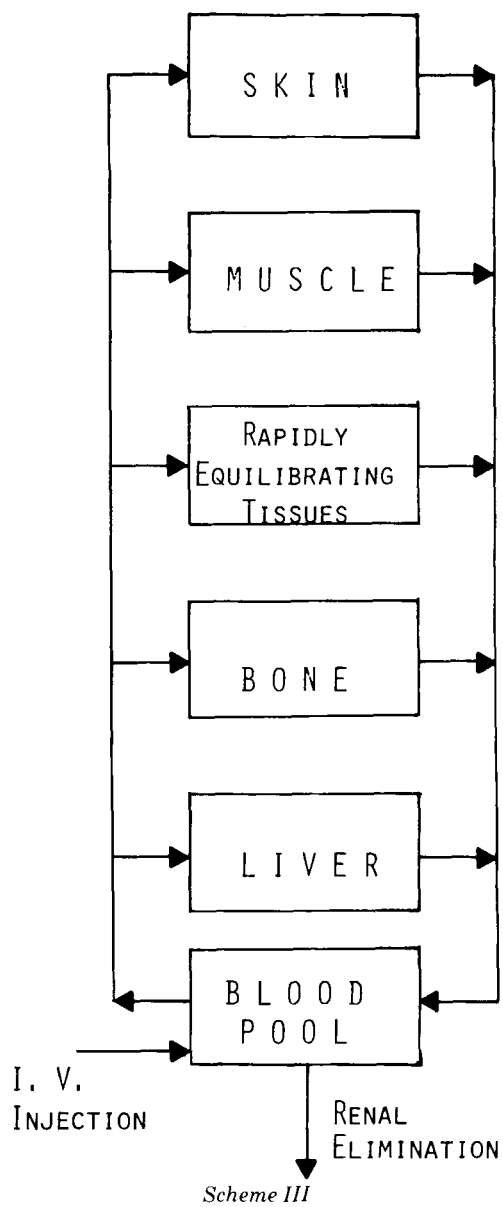
7. Since bone is largely porous mineral substance, the drug is assumed to distribute through the entire tissue.

Assumptions 4 and 5 follow from the work of Okui *et al.* (16) and Kornguth and Kunin (17). These independent studies showed that erythrocytes are relatively impermeable to the cephalosporins. Since the membranes of cells in various tissues are very similar to the membranes of the erythrocytes, cephalosporins probably cannot penetrate into these tissues; *i.e.*, the drug will be restricted to the extracellular water.

For the purpose of characterizing cephalosporin distribution in the body, the following tissue compartments were chosen: skin, which has a large volume compartment and low blood flow; rapidly equilibrating tissues (RET), including the heart and kidneys, which have small volumes and high blood flows; muscle tissue, which has moderate blood flow and intermediate mass; liver, which has large blood flow and intermediate mass; and bone, which is a relatively high-volume, poorly perfused tissue.

The brain was not included in this model because of the lack of penetration of the cephalosporins into the cerebral spinal fluid (18). The fat tissue was also excluded because of the poor lipid solubility of the cephalosporins.

The perfusion model used for the calculation of blood and tissue levels appears in Scheme III. The values used for the blood flows and organ volumes appear in Table I. The contribution of glomerular filtration to



Scheme III

Table II—Pharmacokinetic Parameters for Cephalexin, Cefazolin, and Cephradine Using Two-Compartment Model Analysis

Parameter	Cefazolin	Cephradine	Cephalexin
Dose, g	1.0	2.0	0.5
α, hr^{-1}	4.83 ± 1.78	6.23 ± 1.57	4.64 ± 0.09
β, hr^{-1}	0.57 ± 0.12	0.88 ± 0.13	0.93 ± 0.09
K_{12}, hr^{-1}	1.96 ± 0.94	2.39 ± 0.84	1.27 ± 0.13
K_{21}, hr^{-1}	2.15 ± 0.91	1.73 ± 0.38	2.68 ± 0.22
K_{el}, hr^{-1}	1.30 ± 0.23	2.12 ± 0.63	1.62 ± 0.14
$T_{1/2_\alpha}$, hr	0.17 ± 0.08	0.12 ± 0.03	0.15 ± 0.01
$T_{1/2_\beta}$, hr	1.25 ± 0.26	0.81 ± 0.11	0.75 ± 0.07
V_c, liters	3.48 ± 0.36	10.20 ± 2.01	10.90 ± 0.80
$V_{d_{ss}}$, liters	6.79 ± 1.87	19.02 ± 2.00	16.40 ± 1.20
V_{d_β}, liters	8.15 ± 2.61	23.65 ± 1.25	19.60 ± 1.10
$V_{d_{ext}}$, liters	10.11 ± 3.76	30.70 ± 0.97	24.70 ± 2.00

drug elimination from the body was calculated by assuming a glomerular filtration rate of 120 ml/min for free drug (19) and by calculating the clearance of total drug with the assumption that only free drug is filtered. The active secretion rates, calculated by subtracting the contribution of glomerular filtration from the total drug clearance, were 53, 170, and 240 ml/min for cefazolin, cephalexin, and cephradine, respectively.

A differential equation describing the concentration of drug in a tissue compartment can be written as:

$$V_{\text{tiss}} \frac{d(C_{\text{tiss}})}{dt} = Q_{\text{tiss}}(C_f - C_{\text{tiss}}) \qquad \text{(Eq. 4)}$$

where V_{tiss} and Q_{tiss} represent the volumes of the tissue and plasma flow to the tissue, respectively; and C_f and C_{tiss} represent the free concentrations of drug in the plasma and tissue, respectively. A differential equation for the total drug concentration, C_t, in the plasma can be written as:

$$V_P \frac{d(C_t)}{dt} = \Sigma Q_{\text{tiss}_i}(C_{\text{tiss}_i} - C_f) - \text{GFR}C_f - \text{AS}C_t \qquad \text{(Eq. 5)}$$

where V_P and Q_{tiss_i} represent the plasma volume and plasma flow to the ith tissue, respectively; and C_f represents the free concentration of drug in the plasma. Elimination of drug from the body is included in the terms GFR and AS, the glomerular filtration and active secretion rates, respectively. Equation 5, a differential equation describing the rate of change of total drug in plasma, can be transformed (see *Appendix*) to give a differential equation for the free concentration of drug in the plasma:

$$V_P \frac{d(C_f)}{dt} = \frac{\Sigma Q_{\text{tiss}_i}(C_{\text{tiss}_i} - C_f) - \text{GFR}C_f - \text{AS}C_t}{1 + \dfrac{n_1 K_{a_1} P}{(1 + K_{a_1} C_f)^2} + \dfrac{n_2 K_{a_2} P}{(1 + K_{a_2} C_f)^2}} \qquad \text{(Eq. 6)}$$

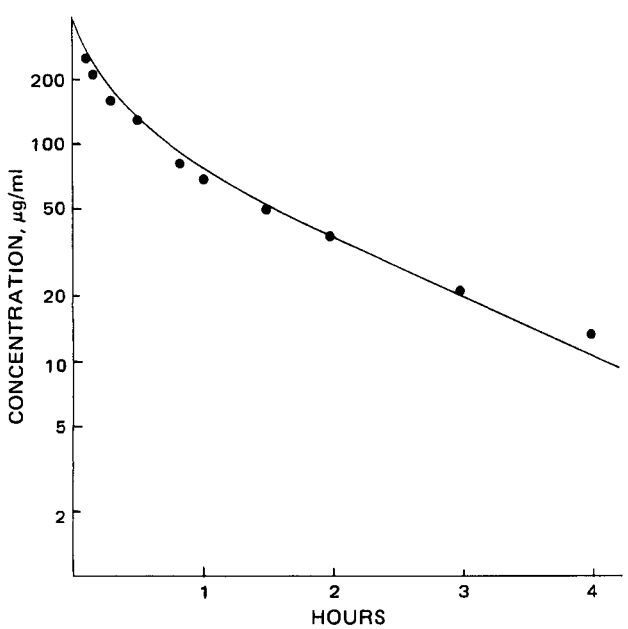


Figure 4—*Serum cefazolin concentration* versus *time fit using two-compartment open model with protein binding.*

Table III—Pharmacokinetic Parameters for Cefazolin Using Two-Compartment Model with Protein Binding

Parameter	Value
K_{12}, hr^{-1}	7.25 ± 23.50
K_{21}, hr^{-1}	1.00 ± 16.09
K_{el}, hr^{-1}	1.15 ± 145.11
V_c, liters	4.04 ± 51.07

in which C_{tiss} represents the free concentration of drug in the tissue.

Differential equations in the form of Eq. 4 were written for each tissue compartment, and Eq. 6 was used to describe the free plasma concentration of drug. The values for protein binding parameters for cefazolin obtained from continuous ultrafiltration experiments were 0.1 and 0.85 mole for n_1 and n_2, respectively. The 0.1-mole value of n_1 may indicate that this binding site represents binding to a protein species less abundant than serum albumin. The affinity constants K_{a_1} and K_{a_2} were 2.67×10^5 and 2.4×10^4 liters/mole, respectively. An albumin concentration of 5.97×10^{-4} M was assumed for all calculations. Both cephalexin and cephradine were assumed to be completely in the free form since the binding was less than 10% at normal therapeutic concentrations.

RESULTS AND DISCUSSION

Two-Compartment Model Analysis of Cephalosporin Data—Semilog plots of the serum concentration of cephalexin (Fig. 1), cephradine (Fig. 2), and cefazolin (Fig. 3) *versus* time all were nonlinear, indicating that a one-compartment model would not adequately describe the pharmacokinetics of these cephalosporins (11). Therefore, a two-compartment model (Scheme I) was used.

All two-compartment model analyses were performed using the NONLIN nonlinear least-squares regression program (20). The integrated forms of the two-compartment model equations were used for all data fitting (1). It was assumed that elimination and distribution were first-order processes, the rate being proportional to the total drug concentration. All serum levels were in terms of total levels, and no attempt was made to correct for any form of drug binding.

The parameters obtained for the fits of the two-compartment model equations to the blood level data from cefazolin, cephalexin, and cephradine after intravenous doses appear in Table II. All correlation

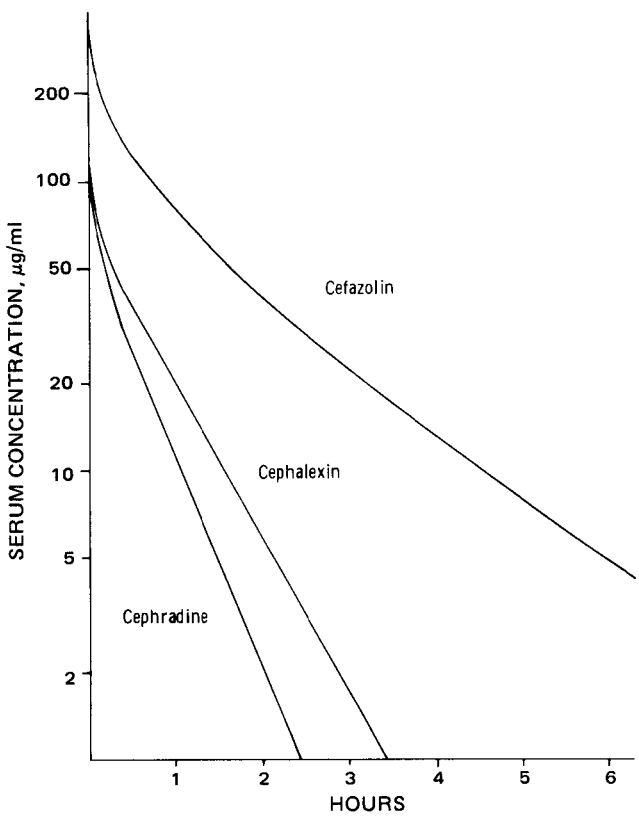


Figure 5—*Calculated serum levels for cefazolin, cephradine, and cephalexin using perfusion model after a 1-g iv dose.*

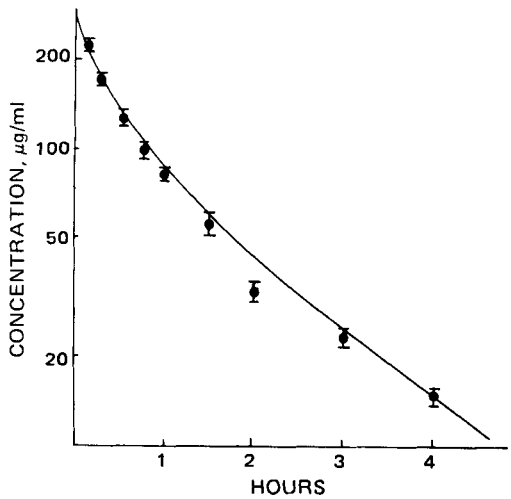


Figure 6—*Serum cefazolin levels in humans after a 1-g iv dose. Key:—, calculated levels of cefazolin using perfusion model; and ●, experimental serum drug levels.*

coefficients exceeded 0.98, indicating excellent fits of the model to the experimental data. A comparison of the volume of distribution for cefazolin with cephradine and cephalexin demonstrates the effect of protein binding on this parameter. The decreased volume of distribution of cefazolin accounts for the higher serum levels that have been found for this drug.

The clearance of these cephalosporins was calculated using the formula:

$$\text{clearance} = K_{el}V_c \qquad \text{(Eq. 7)}$$

The clearances for cefazolin, cephalexin, and cephradine were 75.4, 294, and 364 ml/min, respectively. The low value reported for the clearance of cefazolin in comparison to the other cephalosporins may be due to the high fraction of the drug present in the bound form.

Two-Compartment Model with Protein Binding for Cefazolin—The two-compartment model without protein binding adequately described the blood levels of all of the cephalosporins studied. However, since cefazolin is approximately 80–90% protein bound at normal therapeutic concentrations, a two-compartment model with protein binding was investigated. Because of problems associated with obtaining fits of Eq. 2 to the experimental data, it was possible to fit data from only one of the five subjects. The parameters obtained from this fit are listed in Table III. The NONLIN program was unable to converge to suitable

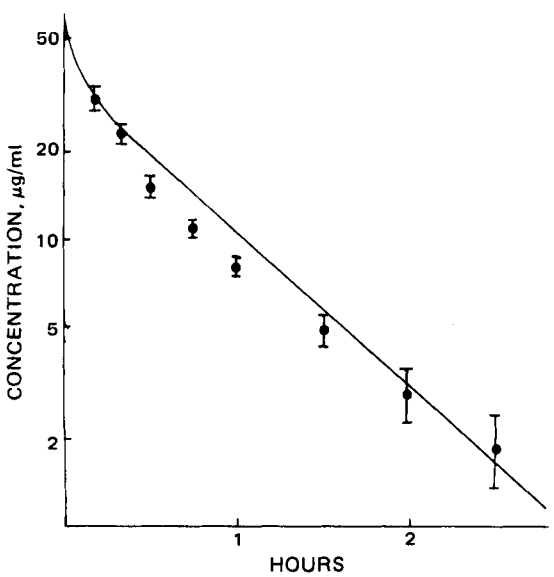


Figure 7—*Serum cephalexin levels in humans after a 0.5-g iv dose. Key: —, calculated levels of cephalexin using perfusion model; and ●, experimental serum drug levels.*

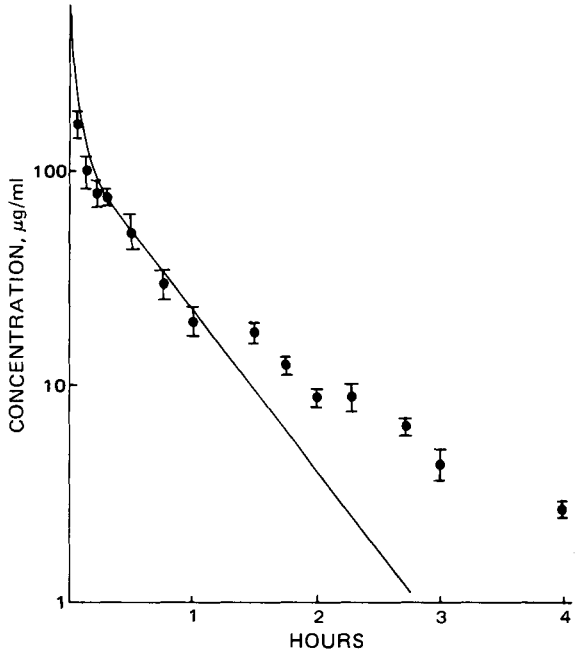


Figure 8—*Serum cephradine levels in humans after a 2-g iv dose. Key: —, calculated levels of cephradine using perfusion model; and ●, experimental serum drug levels.*

estimates for the parameters within 20 iterations for the other four subjects. Adjustment of the initial estimates did little to improve the fit of the equation to the data. A plot of calculated and experimental data for the subject fit by this model appears in Fig. 4. The parameters n_1, n_2, K_{a_1}, and K_{a_2} represent protein binding parameters and were not fitted parameters. The parameters K_{12}, K_{21}, K_{el}, and V_c were fitted to the data.

Examination of Table III shows that the parameters have extremely large standard deviations. Since only one set of data was fit and the standard deviations were unacceptably large, it was concluded that this model could not adequately fit the data using the NONLIN (20) program.

Perfusion Model Predictions of Cephalosporin Levels—The calculated serum levels for a 1-g dose of cefazolin, cephradine, and cephalexin appear in Fig. 5. Comparison of the calculated serum levels using the perfusion model with actual data for cefazolin (Fig. 6) and cephalexin (Fig. 7) demonstrates that this model adequately predicts the serum levels for these drugs.

The perfusion model also predicted the levels for cephradine (Fig. 8) for the first 1.5 hr after administration. However, after 1.5 hr, the experimental data were consistently higher than the predicted line. This deviation between the two curves may be attributable to an overestimate of cephradine clearance in the perfusion model.

The perfusion model was designed for any drug with the characteristics outlined in the previously stated assumptions. For cefazolin, the model was adjusted to account for protein binding. The excellent fit of the data to the predicted curve suggests that these drugs are basically "handled" in a similar fashion by the body and that their different pharmacokinetic profiles are mainly a function of protein binding.

The results of this study show that the two-compartment model with protein binding could not adequately describe the data, probably because the model is a complex nonlinear model.

The two-compartment model and the flow model were equally effective in describing the serum data.

APPENDIX

The equation for the change in total drug as a function of time is Eq. 5. The change in total drug as a function of time can be written as:

$$\frac{d(C_t)}{dt} = \frac{d(C_B)}{dt} + \frac{d(C_f)}{dt} \qquad \text{(Eq. A1)}$$

since:

$$C_t = C_B + C_f \qquad \text{(Eq. A2)}$$

where C_t, C_B, and C_f represent the concentrations of total, bound, and free drug, respectively. The concentration of bound drug can be written as shown in Eq. 1. Differentiation of Eq. 1 yields:

$$\frac{d(C_B)}{dt} = \left[\frac{n_1 K_{a_1} P}{(1 + K_{a_1} C_f)^2} + \frac{n_2 K_{a_2} P}{(1 + K_{a_2} C_f)^2}\right] \frac{d(C_f)}{dt} \qquad \text{(Eq. A3)}$$

Substitution of Eqs. A3 and A2 into Eq. 5 yields Eq. 6.

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Stabilization of Sulfisomidine Tablets by Use of Film Coating Containing UV Absorber: Protection of Coloration and Photolytic Degradation from Exaggerated Light

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Abstract □ The effect of model polymer coating films of vinyl acetate, containing oxybenzone as a UV absorber, on the coloration and photolytic degradation of simple sulfisomidine tablets was examined to attempt stabilization of photosensitive solid dosage forms. Coloration of the tablet surface was followed by the tristimulus colorimetric method in the fading tester equipped with a mercury vapor lamp. Photolytic degradation in the UV region was investigated by a new method for measuring the absorption spectra of a crystal sample in the gas phase, *i.e.*, the semi-integral *attenuance spectra*. Two parameters of a film, thickness and concentration of the UV absorber, were varied at every exposure. These physical and chemical changes are discussed in relation to light transmission properties of films.

Keyphrases □ Sulfisomidine tablets—effect of film coating containing UV absorber on coloration and photolytic degradation □ Film coating—containing UV absorber, effect on coloration and photolytic degradation of sulfisomidine tablets □ UV absorber—contained in film coating, effect on coloration and photolytic degradation of sulfisomidine tablets □ Coloration—sulfisomidine tablets, effect of film coating containing UV absorber □ Photolytic degradation—sulfisomidine tablets, effect of film coating containing UV absorber □ Degradation, photolytic—sulfisomidine tablets, effect of film coating containing UV absorber □ Tablets—sulfisomidine, coloration and photolytic degradation, effect of film coating containing UV absorber

Many solid pharmaceutical medicaments exhibit physical or chemical changes because of the radiant energy of light. Light irradiation can cause color development or color fading. From pharmaceutical and therapeutic standpoints, physical changes can be as serious as chemical instability of the active ingredient. Therefore, protection of solid dosage forms under storage from the deleterious effects of light is one problem in quality control.

Pharmaceutical products can be adequately protected by the use of special glass containers, *i.e.*, light-resistant containers specified in pharmacopeias. The protective effect of colored glass on the fading of tablets containing colorants (1, 2) and on the coloration and photolytic degradation of photolabile sulfisomidine tablets (3) has been investigated.

Coating tablets with a polymer film containing UV absorbers may be another method for protection from light. Along with the use of light-resistant containers, this approach should increase the protective effect since the coating is applied to individual tablets. The effect of the protective coating on the photostability of colorants used in the tablet coating also was studied (4–6), but no report dealt with organic active ingredients. One interesting point in such studies of solid-state stability is the relationship shown to exist (3) between the apparent and chemical changes.

The purpose of the present work was to investigate the