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Physiologically Based Pharmacokinetic Model for Digoxin Disposition in Dogs and Its Preliminary Application to Humans

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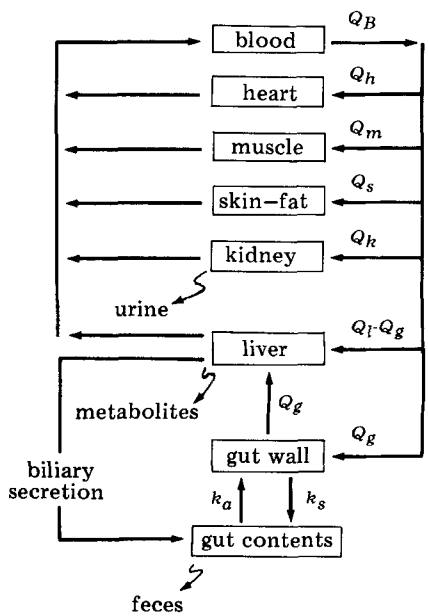
Abstract □ A physiologically based pharmacokinetic model for digoxin disposition developed in the rat was modified to account for the interspecies differences in tissue-to-plasma digoxin concentration ratios and applied to the dog. The model provided a quantitative assessment of the time course of digoxin concentrations in dog plasma, various tissues, and urine. It also predicted the effect of renal failure on digoxin pharmacokinetics in the dog. An attempt to scale the dog model to humans by simply considering differences in organ volumes, organ flow rates, and digoxin clearances was partially successful. Good predictions of plasma digoxin concentration and urinary digoxin excretion after a single dose and of steady-state plasma, heart, and skeletal muscle digoxin concentrations were obtained. However, the model predicted considerably higher kidney digoxin concentrations than are actually found. Although the model adequately characterized the time course of digoxin concentrations in patients with moderate renal impairment, it provided a relatively poor fit to that observed in anuric patients.

Keyphrases □ Digoxin—pharmacokinetic model for disposition in dog developed, applied to humans □ Pharmacokinetics—digoxin, model for disposition in dog developed, applied to humans □ Models, pharmacokinetic—for digoxin disposition in dog, developed, applied to humans □ Cardiotonic agents—digoxin, pharmacokinetic model for disposition in dog developed, applied to humans

Two- and three-compartment open models based on curve fits of plasma concentration–time data are commonly used to describe digoxin pharmacokinetics in humans and other species (1–4). Although these models are useful for clinical application, the basic information that they provide regarding distribution and elimination is intrinsically limited. Transfer rate constants calculated from such models have a high degree of uncertainty (5). Moreover, compartment volumes and transfer rate constants derived from these models have no anatomical or physiological reality. Neither the drug concentrations nor the time course of drug concentrations in particular target tissues other than the plasma can be predicted.

Recently, there has been an interest in the development of physiologically realistic pharmacokinetic models for drug disposition based on organ volumes and blood perfusion rates. In principle, these models permit the prediction of drug concentrations in any tissue at any time and may provide considerable insight to drug dynamics. Another useful feature of these models is that drug disposition in certain pathophysiological conditions may be simulated by altering estimates of organ blood flow (6, 7), drug clearance (8), or drug binding to tissues. Furthermore, under certain conditions, physiologically based models can be scaled to apply to more than one species (9). Therefore, for certain drugs, the large data base needed to develop a physiological pharmacokinetic model may be acquired in a laboratory animal and scaled to apply to humans. This approach has been used with several drugs (6, 10–13).

A detailed physiological model (Scheme I) recently was developed to describe digoxin pharmacokinetics in the rat



Scheme I

Table I—Physiological and Experimental Constants for Digoxin Distribution

Tissue	Volume[a], liters		Blood Flow, liters/hr		R_i[d]
	Dog	Human	Dog[b]	Human[c]	
Blood	0.5	5.4	—	—	—
Heart	0.05	0.3	3	15	40
Skeletal muscle	5.0	30.0	12	75	9
Skin, fat, *etc.*[e]	3.5	30.0	12	75	9
Kidney	0.05	0.3	12	80	200
Liver	0.25	1.5	24	100	15
GI tissues	0.24	1.0	18	70	30
GI contents	0.42	1.7	—	—	—

[a] Values for a 10-kg dog and a 70-kg human (11, 29, 40). [b] Total blood flow = 63 liters/hr (41, 42). [c] Total blood flow = 345 liters/hr (6, 40). [d] Tissue-to-plasma digoxin concentration ratios; values estimated in the dog (17, 18). [e] Lump compartment incorporating all other body regions.

(8). This model describes the time course of plasma and tissue digoxin concentrations in normal rats as well as the time course of plasma digoxin concentrations in rats with ligated bile ducts or ligated ureters. The model also predicts successfully the time course of urinary digoxin excretion in normal and bile duct-ligated rats.

Although the pharmacokinetic model is a qualitatively accurate representation of digoxin disposition not only in the rat but also in other species, including humans, direct quantitative scale-up was not possible because of substantial differences in tissue-to-plasma digoxin concentration ratios between rats and humans (8). For example, rat kidneys and heart show little ability to concentrate digoxin whereas kidney-to-plasma and heart-to-plasma digoxin concentration ratios in humans exceed 30 (14). The present report concerns efforts to develop a physiological pharmacokinetic model for digoxin disposition in the dog, a species in which digoxin distribution appears similar to that observed in humans, and to extend this model to humans.

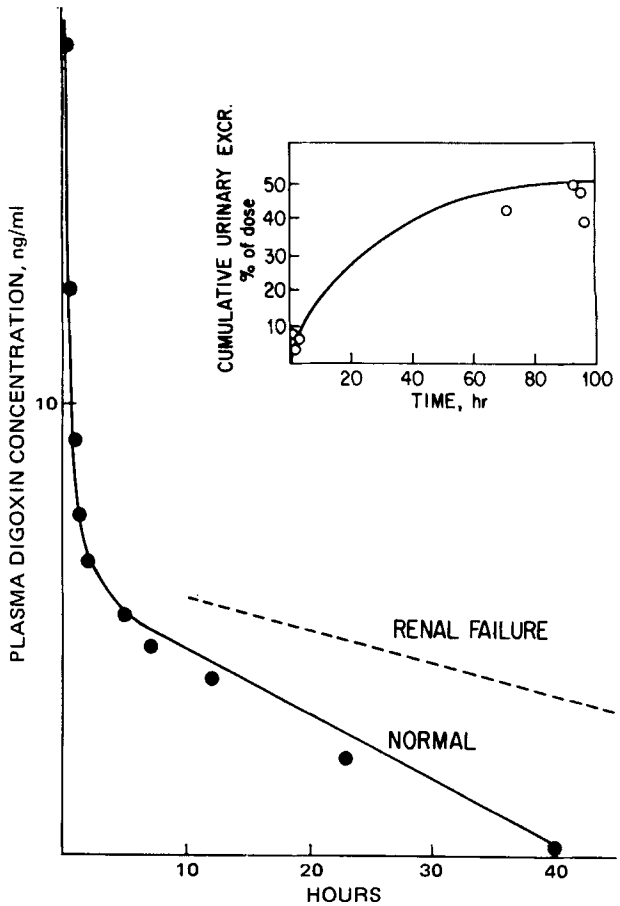


Figure 1—*Predicted plasma digoxin concentrations in normal (—) and ureter-ligated (- - -) dogs after a 50-μg/kg iv dose. The closed circles are data from dogs given the same dose (from Ref. 17). The inset shows the predicted (—) and observed (○) cumulative urinary excretion in the dog after a single dose. Experimental data were taken from Refs. 46–48.*

EXPERIMENTAL

The model shown in Scheme I adequately describes the pharmacokinetics of digoxin disposition in the rat. *A priori,* the same model seemed to be a reasonable choice for the dog and human. This model assumes that each tissue acts as a well-stirred compartment, that drug distribution is blood flow rate limited, that tissue-to-plasma digoxin concentration ratios are independent of drug concentration, and that all rate processes are linear.

A mathematical description of the model is given in the *Appendix*. The concentration of a drug in a tissue, C_i, depends on the volume of the tissue, V_i, the blood flow through the tissue, Q_i, the drug concentration in the blood, C_B, the binding of the drug in the tissue relative to its binding in the blood, R_i, and the tissue's ability to eliminate or clear the drug irreversibly, K_i, *i.e.*:

$$V_i(dC_i/dt) = Q_i[C_B - (C_i/R_i)] - K_iC_i/R_i \qquad \text{(Eq. 1)}$$

Organ volumes and blood flow rates for a 10-kg dog and for a 70-kg human are given in Table I. Since digoxin has little effect on cardiac output (15, 16), blood flow rate values are those estimated in normal individuals. Also listed in Table I are tissue-to-plasma digoxin concentration ratios determined during steady-state studies in dogs (17, 18).

Table II—Clearance and Rate Constants for Digoxin Disposition

Parameter	Estimate	
	Dog	Human
Renal clearance	2.4 liters/hr	7.5 liters/hr
Hepatic clearance	0.8 liter/hr	2.5 liters/hr
Biliary clearance	0.5 liter/hr	1.5 liters/hr
GI clearance	0.04 liter/hr	0.05 liter/hr
Absorption rate constant	0.22 hr^{-1}	0.22 hr^{-1}
Secretion rate constant	0.44 hr^{-1}	0.44 hr^{-1}

Estimates of the required clearance parameters and rate constants are listed in Table II. Renal clearance of digoxin was assumed to be equal to the glomerular filtration rate (19, 20); the net contribution of tubular secretion (21) and reabsorption (22) was considered negligible. The total body clearance of digoxin in each species was estimated from plasma or serum digoxin concentration data after intravenous injection (2, 3, 17, 21). Metabolic clearance was assumed to be the difference between total body clearance and renal clearance. Biliary clearance was estimated from literature data (18, 23).

Initial estimates of fecal clearance of digoxin for dogs and humans were about 0.02 and 0.05 liter/hr, respectively. These values were calculated by assuming a 20-hr half-life for gut transit for both species (24, 25). For the dog, however, simulations based on this estimate resulted in higher digoxin concentration in the plasma and in higher urinary excretion rates than those observed in various studies. After testing several estimates, a value of 0.04 liter/hr was selected. The need for a higher estimate of fecal clearance suggests that digoxin transit from the absorption site(s) is faster than the average transit of fluid through the gut or that other processes, such as gut or bacterial metabolism, contribute to the elimination of digoxin from the GI tract.

The absorption half-life for digoxin was assumed to be 1 hr for both species (26). The rate constant for GI secretion was set equal to twice the absorption rate constant based on previous studies in the rat (8).

The mass balance equations described in the *Appendix* and the constants listed in Tables I and II served as input for a digital computer analog simulation program (27) to calculate digoxin concentrations in the various model compartments. Predicted digoxin concentrations in blood were assumed equal to those in plasma since the blood/plasma digoxin concentration ratio is about unity in both dogs and humans (28). Steady-state digoxin levels were simulated by incorporating a zero-order

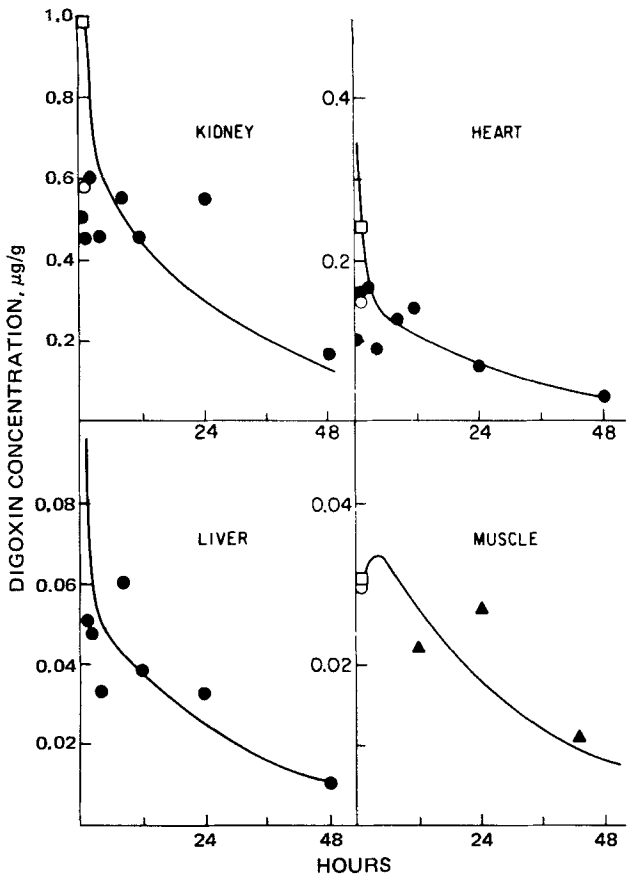


Figure 2—*Predicted (—) and observed digoxin concentrations in different tissues after a 50-μg/kg iv dose to normal dogs. Experimental data were taken from Refs. 17 (●), 47 (▲), 31 (○), and 48 (□).*

input function into the appropriate equations listed in the *Appendix*.

Literature values for plasma and tissue digoxin concentrations in the dog were based on total tritium assays. Most literature references for plasma and tissue digoxin levels in humans utilized either radioimmunoassay or ^{86}Rb-uptake measurements. Reported values in Refs. 1, 18, 19, and 29–31 were based on total tritium analyses. In all cases in which

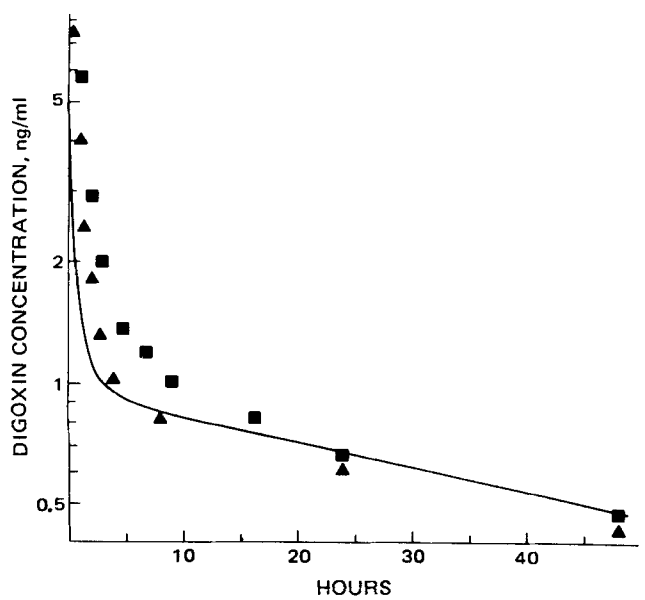


Figure 3—*Predicted (—) and observed plasma digoxin concentrations in adults given a 0.75-mg iv dose. Experimental data were taken from Refs. 34 (▲) and 36 (■).*

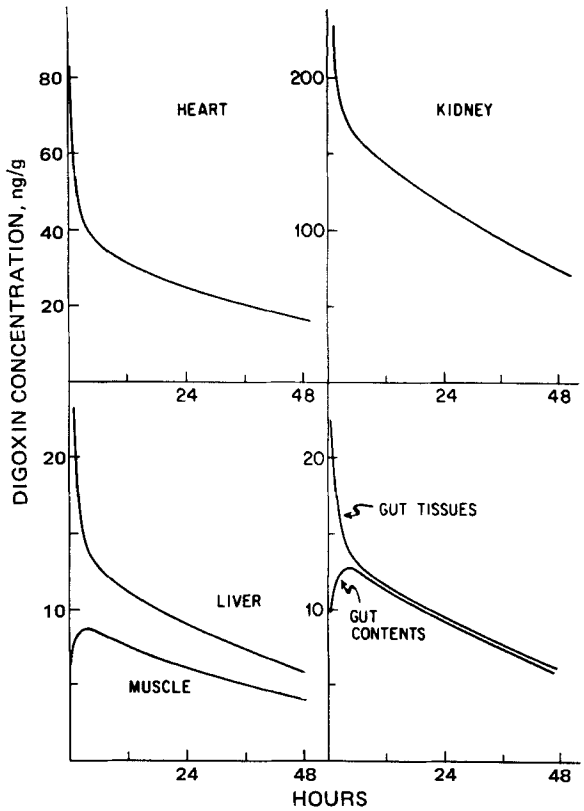


Figure 4—*Predicted tissue digoxin concentrations in adults given a single 0.75-mg iv dose.*

renal function was normal, the values probably closely reflect unchanged digoxin concentrations.

RESULTS AND DISCUSSION

Predicted digoxin concentrations in the plasma and in certain tissues of the dog after a 50-μg/kg iv dose are compared to observed values in Figs. 1 and 2. In general, good agreement is noted. The model also provided a reasonably good prediction of the urinary excretion of digoxin in the dog (inset in Fig. 1).

A pharmacokinetic model for digoxin disposition in dogs with renal failure was developed by setting renal clearance equal to zero but maintaining all other parameters constant. The postdistributive plasma digoxin concentrations after a single intravenous dose, as predicted by the

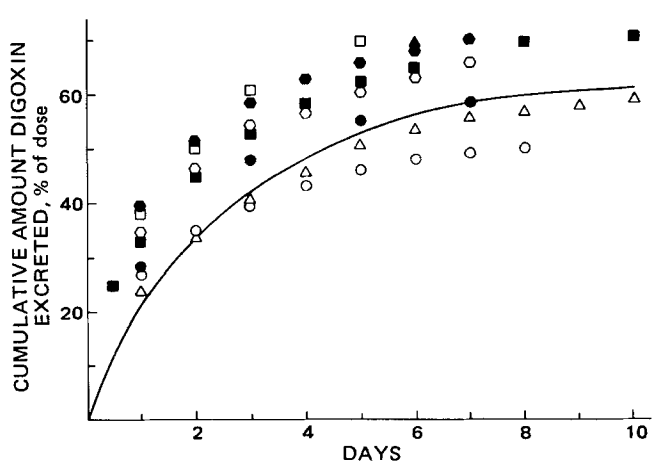


Figure 5—*Predicted (—) and observed cumulative urinary excretion of digoxin in adults after an intravenous dose. Experimental data were taken from Refs. 19 (●), 1 (□), 29 (●), 34 (▲), 35 (△), 36 (■), 30 (○), and 38 (○).*

Table III—Observed and Predicted Steady-State Digoxin Concentrations[a] (Nanograms per Gram) in Various Tissues of Patients Receiving Digoxin Maintenance Therapy

Number of Patients	Plasma Digoxin Concentration, ng/ml	Heart[b]	Skeletal Muscle	Liver	Kidneys	Reference
		Observed				
3	1.3–2.3	LV = 58 ± 18 RV = 47 ± 13 LA = 19 ± 7	8 ± 2	33 ± 6	94 ± 54	33
12	0.9–1.9	V = 133 ± 16 A = 65 ± 9	30 ± 4	72 ± 13	128 ± 20	14
4	1.0–2.5	95 ± 30	9 ± 2	—	—	43
12	1.0–2.3	86 ± 41	—	—	—	32
10	0.9–2.4	31 ± 13	—	—	—	44
8	1.0–2.2	107 ± 33	—	—	—	45
		Predicted				
—	0.9–2.5	36–100	8–23	14–38	180–500	—

[a] Concentration ± *SD*. [b] LV = left ventricle, RV = right ventricle, LA = left atrium, V = ventricle, and A = atrium.

modified model, are shown in Fig. 1. The pharmacokinetic model indicates that both plasma and tissue digoxin concentrations are elevated in the anuric dog compared to those in the dog with normal renal function. These findings are consistent with experimental observations in dogs with ligated ureters (18).

The physiologically based pharmacokinetic model developed for the dog was scaled to apply to humans by adjusting only organ blood flow rates, organ volumes, and clearance parameters (Tables I and II). Predicted and observed plasma digoxin concentrations in adults given a 0.75-mg iv dose are compared in Fig. 3. Although the model predictions underestimate the early digoxin concentrations, good agreement is seen after 10 hr. Many reasons are possible for the initially poor predictions. Estimates of average blood flows and tissue-to-plasma concentration ratios (Table I) or of average biliary clearance (Table II) may be too high to reflect accurately the situation in these patients. Alternatively, diffusion of drug to the intracellular space may play a more important role than is assumed by a blood flow rate-limited distribution model.

The predicted tissue digoxin concentrations in humans after a single intravenous dose, based on tissue-to-plasma digoxin concentration ratios estimated in the dog, are shown in Fig. 4. Unfortunately, there are little published data to compare with these values. However, postmortem measurements of tissue digoxin levels in patients who had been receiving digoxin maintenance therapy and who had plasma digoxin concentrations of 0.9–1.9 ng/ml (14, 32, 33) are in good agreement with predicted steady-state digoxin levels in plasma, heart, and skeletal muscle (Table III). Postmortem digoxin concentrations in the liver are about 1.5–2 times greater than those predicted. A larger difference was noted between observed and predicted digoxin concentrations in the kidney; predicted digoxin levels are two to three times higher than those found.

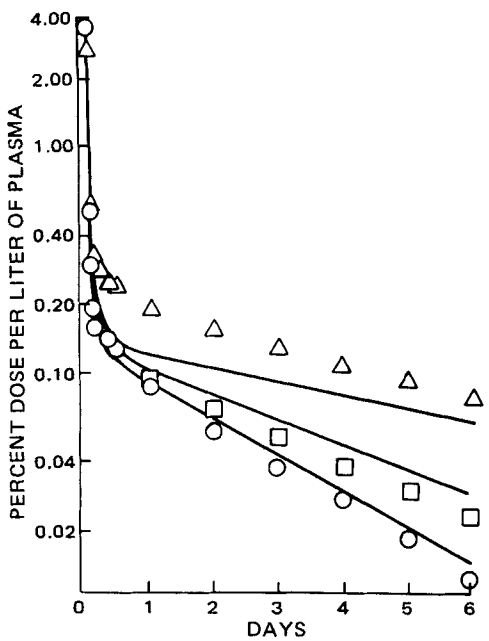


Figure 6—*Predicted (—) and observed plasma digoxin concentrations in patients with normal renal function (○), in patients with moderate renal impairment (□), and in patients with severe renal failure (△). Experimental data were taken from Ref. 19.*

A wide range of results has been reported for the urinary digoxin excretion in patients with normal renal function (1, 19, 29–31, 34–36). The predicted urinary excretion rate of digoxin is consistent with these data (Fig. 5).

An effort to simulate plasma digoxin concentrations in patients with impaired renal function by simply reducing the renal clearance parameter of the model was only partially successful. Figure 6 shows predicted and observed plasma digoxin levels after a single intravenous dose to patients with different degrees of renal function. Reasonably good predictions of plasma digoxin concentrations are seen for patients with normal renal function and with moderate renal impairment, *i.e.*, renal function about 50% of normal. However, the predicted plasma digoxin levels of anephric patients consistently underestimate the observed values. This discrepancy may be related in part to the fact that uremia also decreases the binding of digoxin to myocardial tissue (37) as well as its apparent volume of distribution (3, 38). More importantly, it undoubtedly reflects the use of a nonspecific assay that measures digoxin as well as all its metabolites that accumulate in the absence of renal function, thus overestimating digoxin concentration.

In conclusion, the present pharmacokinetic model requires significant modification before it can be used to describe the average time course of digoxin in humans. It is also evident, at least with digoxin, that it is not reasonable to assume that tissue-to-plasma drug concentration ratios are similar in different species. Scaling of physiological models must routinely consider such differences.

APPENDIX

The following mass balance–blood flow equations describe the concentrations in each compartment of the pharmacokinetic model shown in Scheme I:

$$V_B(dC_B/dt) = (Q_hC_h/R_h) + (Q_mC_m/R_m) + (Q_sC_s/R_s) + (Q_kC_k/R_k) + (Q_lC_l/R_l) - Q_BC_B \quad \text{(Eq. A1)}$$

$$V_h(dC_h/dt) = Q_h[C_B - (C_h/R_h)] \quad \text{(Eq. A2)}$$

$$V_m(dC_m/dt) = Q_m[C_B - (C_m/R_m)] \quad \text{(Eq. A3)}$$

$$V_s(dC_s/dt) = Q_s[C_B - (C_s/R_s)] \quad \text{(Eq. A4)}$$

$$V_k(dC_k/dt) = Q_k[C_B - (C_k/R_k)] - (K_kC_k/R_k) \quad \text{(Eq. A5)}$$

$$V_l(dC_l/dt) = (Q_l - Q_g)C_B + (Q_gC_g/R_g) - (Q_lC_l/R_l) - (K_lC_l/R_l) - (K_bC_l/R_l) \quad \text{(Eq. A6)}$$

$$V_g(dC_g/dt) = Q_g[C_B - (C_g/R_g)] + k_aV_cC_c - k_sV_gC_g \quad \text{(Eq. A7)}$$

$$V_c(dC_c/dt) = k_sV_gC_g + (K_bC_l/R_l) - k_aV_cC_c - K_gC_c \quad \text{(Eq. A8)}$$

where K_k, K_l, K_b, and K_g represent renal, metabolic, biliary, and GI clearances, respectively; and k_a and k_s represent first-order rate constants for GI absorption and secretion, respectively. The terms V_i, C_i, Q_i, and R_i represent tissue volumes, drug concentrations, blood flow rates, and tissue-to-blood partition coefficients, respectively. The subscripts of these terms are as follows: B = blood; h = heart; m = skeletal muscle; s = skin, fat, *etc.*; k = kidney; l = liver; g = GI tissues; and c = GI contents.

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