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Pharmacokinetic Model for Salicylate in Cerebrospinal Fluid, Blood, Organs, and Tissues

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Abstract □ The developed pharmacokinetic model, an extension of the Bischoff–Dedrick model, simultaneously predicts the kinetic behavior of salicylate in cerebrospinal fluid, blood, organs, and tissues. The model, which is entirely different from conventional compartment models, is derived from basic considerations of drug distribution with biochemical and physiological meaning. The dog was studied at three different dosages of salicylate: therapeutic, moderate intoxication, and severe intoxication. The predicted kinetics of salicylate in cerebrospinal fluid, blood, plasma, liver, muscle, and adipose tissue by the model agreed well with the experimental data. The effectiveness of hemoperfusion treatment for the severely intoxicated dog by albumin-coated activated carbon and its effect on the kinetic behavior of salicylate in cerebrospinal fluid, blood, organs, and tissues were studied. The model was also applied to predict the kinetic changes of salicylate in the body during and after the extracorporeal treatment. The predicted results also agreed with the experimental data.

Keyphrases □ Models, pharmacokinetic—developed to predict behavior of salicylate in cerebrospinal fluid, blood, organs, and tissues, compared to experimental data with dogs □ Pharmacokinetic models—developed to predict behavior of salicylate in cerebrospinal fluid, blood, organs, and tissues, compared to experimental data with dogs □ Salicylate—pharmacokinetic model developed to predict behavior in cerebrospinal fluid, blood, organs, and tissues, compared to experimental data with dogs

Blood or plasma drug levels have been used as an index of dose scheduling for therapeutics under the assumption that the drug level in blood or plasma corresponds to the pharmacological effect of the drug. Conventional pharmacokinetic models have been widely applied to simulate the kinetic behavior of drug levels in blood or plasma. However, the knowledge of drug levels in blood or plasma with time may not provide sufficient information for adequate therapy. The kinetic information of drug levels in brain, cerebrospinal fluid, blood, organs, and tissues of pharmacological interest may be necessary for the development of more appropriate dosage regimens.

The model developed and used in this study is an extension of the Bischoff–Dedrick model (1, 2). This model is derived from basic considerations of drug distribution with biochemical and physiological meaning. The model has been applied successfully to predict the pharmacokinetics of thiopental (2, 3), methotrexate (1, 4, 5), and cytarabine (6).

Previously, an extended version of the Bischoff–Dedrick model was used to predict thiopental kinetics in the dog (2). In this paper, the model previously presented (2) is modified and applied to salicylate in the dog. The model also is modified to consider the effects of activated carbon hemoperfusion on the pharmacokinetics of salicylate in the dog. Since drug–protein binding plays an important role in pharmacological effect and pharmacokinetics, the model also is applied to predict the pharmacokinetics of free (unbound) salicylate levels in plasma water, which is more related to the pharmacological effect of the drug.

THEORETICAL

A diagram of blood circulation through various body regions is shown in Scheme I. The blood pool is the blood volume excluding the blood contained in the capillary beds of organs and tissues in the body.

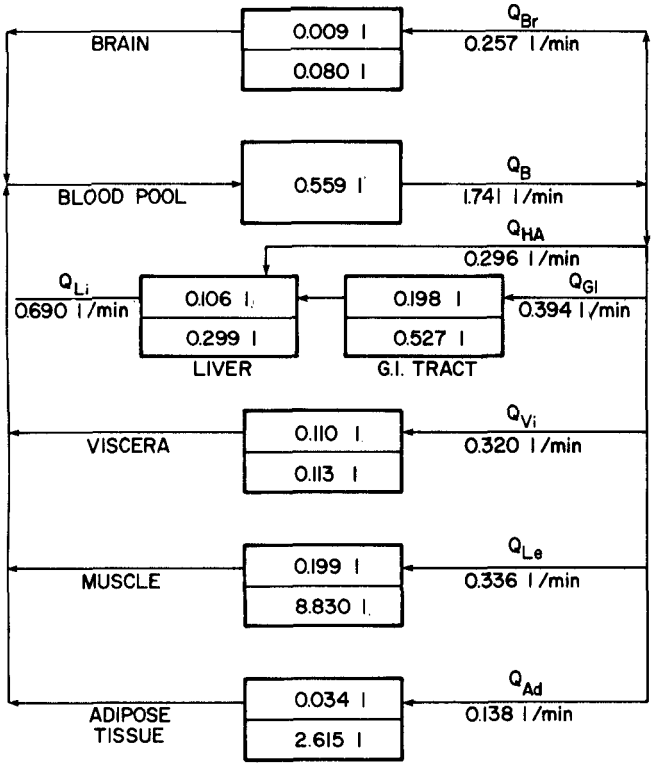
The transient mass balance for any organ or body region can be expressed as (2):

$$\begin{bmatrix}\text{drug accumulation rate}\\ \text{in both capillary bed and}\\ \text{tissue portion}\end{bmatrix} = \begin{bmatrix}\text{drug inflow rate from}\\ \text{blood pool and/or}\\ \text{other body regions}\end{bmatrix} + [\text{drug ingestion rate, if any}] - \begin{bmatrix}\text{drug outflow rate}\\ \text{from body region}\end{bmatrix} - \begin{bmatrix}\text{drug metabolism rate and/or}\\ \text{excretion rate, if any}\end{bmatrix} \quad \text{(Eq. 1)}$$

The mathematical equation of the transient mass balance for any body region (Yz) is:

$$\frac{d(V_{YzB}C_{T,YzB})}{dt} + \frac{d(V_{YzT}C_{T,YzT})}{dt} = Q_{Yz}(C_{T,B} - C_{T,YzB}) \quad \text{(Eq. 2)}$$

where the subscripts mean the following: B, blood; T, total or tissue; and Yz, a body region such as Ad (adipose), Br (brain), GI (gastrointestinal), Li (liver), Mu (muscle), and Vi (viscera); and where $C_{T,B}$ is the total



Scheme I—Body regions and blood flows for a 15-kg (average) dog. Key: l = liters.

(bound and unbound) drug concentration in blood from the blood pool, $C_{T,YzB}$ is the total drug concentration in the capillary bed (blood portion) of the body region (Yz), $C_{T,YzT}$ is the total drug concentration in the tissue portion of the body region (Yz), Q_{Yz} is the blood flow rate from the body region (Yz), t is time, V_{YzB} is the blood volume in the capillary bed of the body region (Yz), and V_{YzT} is the tissue volume in the tissue portion of the body region (Yz).

Most drugs can be bound to plasma proteins, especially to albumin, and to various tissue components (7). The free (unbound) drug level in the target organ(s) is more related to the pharmacological effect of the drug. The model considers this factor by correlating the total drug concentration with the free drug concentration in blood, organs, and tissues. The relationship between the total drug concentration, $C_{T,B}$, and the free drug concentration, $C_{F,B}$, in blood can be determined *in vitro*. Thus:

$$C_{T,B} = f_B(C_{F,B}) \qquad \text{(Eq. 3)}$$

where $f_B(C_{F,B})$ is a mathematical expression of the total drug concentration in terms of the free drug concentration in blood.

The mathematical relation between the total drug concentration, $C_{T,YzB}$, and the free drug concentration, $C_{F,YzB}$, in the blood of any organ capillary bed, YzB, is the same as that in Eq. 3:

$$C_{T,YzB} = f_B(C_{F,YzB}) \qquad \text{(Eq. 4)}$$

Similarly, the total drug concentration, $C_{T,YzT}$, in the tissue portion of the body region, Yz, can be expressed in terms of the corresponding free drug concentration, $C_{F,YzT}$, by another function, $f_{YzT}(C_{F,YzT})$:

$$C_{T,YzT} = f_{YzT}(C_{F,YzT}) \qquad \text{(Eq. 5)}$$

After Eqs. 3–5 are substituted into Eq. 2, Eq. 2 becomes:

$$\frac{d[V_{YzB}f_B(C_{F,YzB})]}{dt} + \frac{d[V_{YzT}f_{YzT}(C_{F,YzT})]}{dt} = Q_{Yz}[f_B(C_{F,B}) - f_B(C_{F,YzB})] \qquad \text{(Eq. 6)}$$

Equation 6 can be developed to the following equation:

$$V_{YzB}f_B'(C_{F,YzB})\frac{dC_{F,YzB}}{dt} + f_B(C_{F,YzB})\frac{dV_{YzB}}{dt} + V_{YzT}f'_{YzT}(C_{F,YzT})\frac{dC_{F,YzT}}{dt} + f_{YzT}(C_{F,YzT})\frac{dV_{YzT}}{dt} = Q_{Yz}[f_B(C_{F,B}) - f_B(C_{F,YzB})] \qquad \text{(Eq. 7)}$$

where $f_B'(C_{F,YzB}) = df_B(C_{F,YzB})/dC_{F,YzB}$ and $f'_{YzT}(C_{F,YzT}) = df_{YzT}(C_{F,YzT})/dC_{F,YzT}$.

Capillaries in organs and tissues differ widely in their permeability characteristics. There are two types of mass transfer between the capillaries and the surrounding tissue. One type is the nearly instantaneous establishment of an equilibrium free drug concentration between the capillaries and the tissue. The capillaries of the liver permit the passage of substances quite readily (8). The equilibrium free drug concentration between the liver capillaries and the surrounding tissue can be established rapidly. In this case, the free drug concentration, $C_{F,YzT}$, in the tissue effectively equals the free drug concentration, $C_{F,YzB}$, in the capillaries. That is:

$$C_{F,YzT} = C_{F,YzB} \qquad \text{(Eq. 8)}$$

Substitution of Eq. 8 into Eq. 5 gives:

$$C_{T,YzT} = f_{YzT}(C_{F,YzB}) \qquad \text{(Eq. 9)}$$

Equations 8 and 9 are substituted into Eq. 7, rearranged, and simplified to:

$$[V_{YzB}f_B'(C_{F,YzB}) + V_{YzT}f'_{YzT}(C_{F,YzB})]\frac{dC_{F,YzB}}{dt} + f_B(C_{F,YzB})\frac{dV_{YzB}}{dt} + f_{YzT}(C_{F,YzB})\frac{dV_{YzT}}{dt} = Q_{Yz}[f_B(C_{F,B}) - f_B(C_{F,YzB})] \qquad \text{(Eq. 10)}$$

The second type of mass transport through the capillary wall is the restricted passage between the capillaries and the tissue. For instance, the capillary wall in muscle is composed of an interlocking mosaic of endothelial cells with slits (junctions) between them that could function as the postulated pores and could account for the restricted passage of water-soluble compounds (9). The restricted transport of salicylate through the muscle capillary wall does not allow the instantaneous establishment of the equilibrium free salicylate concentration between the capillaries and the muscle tissue.

The restricted transport of drugs between the capillaries and the tissue may be described in terms of Fick's law. The changing rate of the free drug concentration, $C_{F,YzT}$, in the tissue is proportional to the free concentration difference between the capillaries and the tissue, which gives:

$$\frac{dC_{F,YzT}}{dt} = P_{Yz}(C_{F,YzB} - C_{F,YzT}) \qquad \text{(Eq. 11)}$$

where P_{Yz} is a proportionality constant called the permeability constant and $C_{F,YzB}$ and $C_{F,YzT}$ are the free drug concentrations in the capillaries and the tissue of the body region, Yz.

Substituting Eq. 11 into Eq. 7 gives:

$$V_{YzB}f_B'(C_{F,YzB})\frac{dC_{F,YzB}}{dt} + f_B(C_{F,YzB})\frac{dV_{YzB}}{dt} + V_{YzT}f'_{YzT}(C_{F,YzT})P_{Yz} \times (C_{F,YzB} - C_{F,YzT}) + f_{YzT}(C_{F,YzT})\frac{dV_{YzT}}{dt} = Q_{Yz}[f_B(C_{F,B}) - f_B(C_{F,YzB})] \qquad \text{(Eq. 12)}$$

MODEL

This study attempted to apply the model to predict the kinetic behavior of salicylate in cerebrospinal fluid, blood, liver, muscle, and adipose tissue because experimental kinetic data of salicylate in these body regions are available (10). At least five body regions may be defined: brain, liver, muscle, adipose tissue, and the blood pool (the blood volume excluding those blood volumes in the capillary beds of body regions). In mammals, blood from the GI area perfuses the liver. Thus, GI tissues are added as another body region. Since there is little interest in the kinetics of salicylate in the kidneys or heart, these two organs may be included in the body region called viscera.

A diagram of blood circulation in the seven body regions with physiological data of blood volumes, tissue volumes, and blood flows for a 15-kg (average) dog is shown in Scheme I. Some physiological data are revised and different from those given previously (2). These revised data represent the actually measured statistical data (11–18).

The transient mass balance for the blood pool can be expressed as:

$$\frac{d(V_{B,t}C_{T,B})}{dt} = (Q_{Br}C_{T,BrB} + Q_{Li}C_{T,LiB} + Q_{Vi}C_{T,ViB} + Q_{Mu}C_{T,MuB} + Q_{Ad}C_{T,AdB}) + Mg(t) - Q_BC_{T,B} \qquad \text{(Eq. 13a)}$$

Table I—Parameters and Constants for the Model[a]

	Blood Pool	Brain	Liver	Viscera	GI Area	Muscle	Adipose Tissue
$F_{V,YzB}$[b]	0.460	0.007	0.087	0.091	0.163	0.164	0.028
$F_{W,YzT}$[c]	—	0.7936	0.7326	0.7824	0.7410	0.7757	0.1922

[a] A (mg/liter) = 72.6645, M = 1.1571, B (mg/liter) = 175.1879, N = 1.2441, P_{CSF} (21, 22) (min^{-1}) = 0.0040, P_{Mu} (8, 23) (min^{-1}) = 4.5550, Q_{BL} (liter/min) = 0.001, Q_{ET} (liter/min) = 0.065, Q_{SE} (liter/min) = 0.00167, Q_{CSF} (8, 23) (ml/min) = 0.08, and V_{CSF} (ml) (8, 23) = 32 for a 15-kg (average) dog. [b] Fraction of the blood volume in organ capillaries to the total blood volume in the body. [c] Taken from Table 1 of Ref. 2.

or:

$$\begin{bmatrix}\text{drug accumulation}\\ \text{rate in blood pool}\end{bmatrix} = \begin{bmatrix}\text{summation of drug inflow rates}\\ \text{from five body regions}\end{bmatrix}$$

$$+ [\text{ingestion rate}] - [\text{drug outflow rate from blood pool}] \quad \text{(Eq. 13}b\text{)}$$

Plasma protein binding of salicylate was studied by the equilibrium dialysis technique (19). A linear relation was found between the total salicylate concentration, $C_{T,P}$, and the free concentration, $C_{F,P}$, in plasma in the range of salicylate levels investigated (10):

$$C_{T,P} = f_P(C_{F,P}) = B + NC_{F,P} \quad \text{(Eq. 14)}$$

where B and N are constants (10) given in Table I.

The relationship between the total salicylate concentration and the free concentration in whole blood may be determined indirectly. Since the free (unbound) drug in plasma water is in equilibrium with the bound drug in both plasma and blood, simultaneous determination of both total salicylate concentrations in blood and plasma from the same samples makes it possible to find the free concentration corresponding to both total concentrations in plasma and blood from Eq. 14. The relation thus constructed between the total salicylate concentration, $C_{T,B0}$, in original (nondiluted) blood and the free concentration, $C_{F,B}$, in blood water is also linear (10):

$$C_{T,B0} = f_B(C_{F,B}) = A + MC_{F,B} \quad \text{(Eq. 15)}$$

The values for A and M are also listed in Table I.

The experimental salicylate distribution data were obtained during a 6-hr experiment (10) in which blood loss occurred due to the surgical trauma from taking tissue samples. Normal saline was given continuously to maintain adequate blood pressure and blood volume. Therefore, the blood in the body was gradually diluted during the experiment. The fraction of whole (nondiluted) blood at time t in the continuously diluted blood, $F_B(t)$, can be calculated from the solution to a differential equation of the mass balance for the whole (nondiluted) blood. The rate of change of the total whole (nondiluted) blood volume in the body is equal to the loss rate of the whole blood, $Q_{BL}F_B(t)$, due to bleeding. It gives:

$$\frac{d[V_{TB,t}F_B(t)]}{dt} = -Q_{BL}F_B(t) \quad \text{(Eq. 16)}$$

where:

$$V_{TB,t} = V_{TB,0} + (Q_{SE} - Q_{BL})t \quad \text{(Eq. 17)}$$

and $F_B(t)$ is the fraction of whole (nondiluted) blood in the continuously diluted blood at time t, Q_{BL} is the blood loss rate due to bleeding from tissues, Q_{SE} is the saline-entering rate to the vein, $V_{TB,0}$ is the total blood volume in the body at time zero, and $V_{TB,t}$ is the total blood volume (diluted blood) in the body at time t.

In this study, the normal saline infusion rate was kept constant while the bleeding rate of blood loss from tissues was assumed to be constant (Table I). After Eq. 17 is substituted into Eq. 16, the solution to Eq. 16, under the conditions of both Q_{SE} and Q_{BL} being constants, gives:

$$F_B(t) = F_B(0)\left[1 + \frac{(Q_{SE} - Q_{BL})t}{V_{TB,0}}\right]^{-[Q_{SE}/(Q_{SE}-Q_{BL})]} \quad \text{(Eq. 18)}$$

Since time zero is the time just prior to blood dilution from saline infusion (10), the fraction of whole (nondiluted) blood at time zero, $F_B(0)$, is one.

The amount of salicylate in the diluted blood equals the amount of salicylate in the whole blood fraction plus that of salicylate in the water fraction of the diluted blood. Thus, it gives:

$$V_{TB,t}C_{T,B} = [V_{TB,t}F_B(t)]C_{T,B0} + \{V_{TB,t}[1 - F_B(t)]\}C_{F,B} \quad \text{(Eq. 19)}$$

Equation 19 may be simplified to:

$$C_{T,B} = F_B(t)C_{T,B0} + [1 - F_B(t)]C_{F,B} \quad \text{(Eq. 20)}$$

Substituting Eq. 15 into Eq. 20 and rearranging give:

$$C_{T,B} = F_B(t)A + H_m(t)C_{F,B} \quad \text{(Eq. 21)}$$

where $H_m(t) = 1 + (M - 1)F_B(t)$, A and M are constants in Eq. 15 and their values are shown in Table I, $C_{F,B}$ is the free salicylate concentration in blood water, $C_{T,B0}$ is the total salicylate concentration in whole (undiluted) blood, and $C_{T,B}$ is the total salicylate concentration in the diluted blood at time t.

Similarly, the total salicylate concentration in the blood of the capillary bed of any body region, Yz, can be expressed as:

$$C_{T,YzB} = F_B(t)A + H_m(t)C_{F,YzB} \quad \text{(Eq. 22)}$$

where $C_{F,YzB}$ is the free salicylate concentration in the capillary blood of any body region, Yz, and $C_{T,YzB}$ is the total salicylate concentration in the capillary blood of any body region, Yz. The blood volume of the blood pool, $V_{B,t}$, at time t can be calculated by:

$$V_{B,t} = V_{B,0} + (Q_{SE} - Q_{BL})tF_{V,B} \quad \text{(Eq. 23)}$$

where $F_{V,B}$ is the fraction of the blood volume of the blood pool in the total blood volume, $V_{B,0}$ is the blood volume of the blood pool at time zero, and $V_{B,t}$ is the blood volume of the blood pool at time t. Substituting Eqs. 21–23 into Eq. 13 and rearranging result in:

$$\frac{dC_{F,B}}{dt} = (Q_{Br}C_{F,BrB} + Q_{Li}C_{F,LiB} + Q_{Vi}C_{F,ViB} + Q_{Mu}C_{F,MuB} + Q_{Ad}C_{F,AdB})/V_{B,t} + Mg(t)/[V_{B,t}H_m(t)] - J_B(t)C_{F,B} - G_B(t) \quad \text{(Eq. 24)}$$

where:

$$G_B(t) = A\{F_B'(t)/H_m(t) + (Q_{SE} - Q_{BL})F_{V,B}F_B(t)/[V_{B,t}H_m(t)]\} \quad \text{(Eq. 25}a\text{)}$$

and:

$$J_B(t) = [H_m'(t)/H_m(t) + (Q_{SE} - Q_{BL})F_{V,B}/V_{B,t} + Q_B/V_B] \quad \text{(Eq. 25}b\text{)}$$

where $F_B'(t) = dF_B(t)/dt$; $H_m'(t) = dH_m(t)/dt$; $C_{F,B}$ is the free salicylate concentration in the blood pool; $C_{F,YzB}$ is the free salicylate concentration in the capillary bed of any body region, Yz; Q_{Yz} is the blood flow rate from the body region, Yz; and $V_{B,t}$ is the blood volume of the blood pool at time t.

An infusion pump was used to infuse the drug solution at a constant rate over 5 min (10). Thus, the ingestion term, $Mg(t)$, in Eq. 24 is equal to the dose divided by 5.

Liver—The transient mass balance for the liver (Li) is:

$$\frac{d(V_{LiB,t}C_{T,LiB})}{dt} + \frac{d(V_{LiT}C_{T,LiT})}{dt} = (Q_{HA}C_{T,B} + Q_{GI}C_{T,GIB}) - Q_{Li}C_{T,LiB} - R_m \quad \text{(Eq. 26}a\text{)}$$

or:

$$\begin{bmatrix}\text{drug accumulation rate}\\ \text{in capillary bed and}\\ \text{tissue portion of liver}\end{bmatrix} = \begin{bmatrix}\text{drug inflow rates from}\\ \text{blood pool (hepatic artery) and}\\ \text{GI tissue (portal vein)}\end{bmatrix} - \begin{bmatrix}\text{drug outflow}\\ \text{rate from liver}\end{bmatrix} - [\text{metabolism rate}] \quad \text{(Eq. 26}b\text{)}$$

Salicylate did not bind with the tissue components of the liver (10), which suggests that the amount of salicylate in the liver tissue equals the free salicylate concentration, $C_{F,LiT}$, multiplied by the volume of liver tissue water, $V_{LiT}F_{w,LiT}$:

$$V_{LiT}C_{T,LiT} = (V_{LiT}F_{w,LiT})C_{F,LiT} \quad \text{(Eq. 27)}$$

where $C_{F,LiT}$ and $C_{T,LiT}$ are the free and total salicylate concentrations

in the tissue portion of the liver, respectively; $F_{w,LiT}$ is the volume fraction of water in the tissue portion of the liver; and V_{LiT} is the volume of the tissue portion of the liver. Since the liver capillaries are highly permeable to salicylate, the equilibrium salicylate concentration (unbound concentration) between the capillaries and the liver tissue may be established nearly instantaneously:

$$C_{F,LiT} = C_{F,LiB} \quad \text{(Eq. 28)}$$

Substitution of Eq. 28 into Eq. 27 yields:

$$V_{LiT}C_{T,LiT} = (V_{LiT}F_{w,LiT})C_{F,LiB} \quad \text{(Eq. 29)}$$

The total salicylate concentration, $C_{T,LiB}$, and the blood volume, $V_{LiB,t}$, in the liver capillaries at time t have similar formulas as those in Eqs. 22 and 23:

$$C_{T,LiB} = F_B(t)A + H_m(t)C_{F,LiB} \quad \text{(Eq. 30)}$$

and:

$$V_{LiB,t} = V_{LiB,0} + (Q_{SE} - Q_{BL})tF_{V,LiB} \quad \text{(Eq. 31)}$$

where $F_{V,LiB}$ is the fraction of the blood volume of the liver capillary bed in the total blood volume, and $V_{LiB,0}$ and $V_{LiB,t}$ are the blood volumes of the liver capillary bed at time zero and t, respectively.

Substituting Eqs. 29–31 into Eq. 26*a* and rearranging yield:

$$\frac{dC_{F,LiB}}{dt} = (Q_{HA}C_{F,B} + Q_{GI}C_{F,GIB})H_m(t)/L_{Li}(t) - J_{Li}(t)C_{F,LiB} - R_m/L_{Li}(t) - G_{Li}(t) \quad \text{(Eq. 32)}$$

where:

$$L_{Li}(t) = V_{LiB,t}H_m(t) + V_{LiT}F_{w,LiT}$$

$$G_{Li}(t) = A[V_{LiB,t}F_B'(t) + (Q_{SE} - Q_{BL})F_{V,LiB}F_B(t)]/L_{Li}(t)$$

$$J_{Li}(t) = [V_{LiB,t}H_m'(t) + (Q_{SE} - Q_{BL})F_{V,LiB}H_m(t) + Q_{Li}H_m(t)]/L_{Li}(t)$$

Q_{HA} = blood flow rate of the hepatic artery

Q_{GI} = blood flow rate from the GI body region

The metabolism rate, R_m, can generally be described in terms of the simple Michaelis–Menten form:

$$R_m = \frac{K_{Li}C_{F,LiT}}{K_{M,Li} + C_{F,LiT}} \quad \text{(Eq. 33)}$$

There are two special cases: (*a*) if $C_{F,LiT} \gg K_{M,Li}$, then $R_m = K_{Li}$ (zero order), and (*b*) if $C_{F,LiT} \ll K_{M,Li}$, then $R_m = (K_{Li}/K_{M,Li})C_{F,LiT}$ (first order).

Since the metabolism mainly occurs in the liver, it was assumed that all salicylate metabolism occurs in the liver. In general, similar terms could be added to the other body regions if necessary. It was found previously (10) that the total excretion rate of unchanged salicylate and its metabolites (salicylurate, salicylglucuronide, and gentisate) was zero order and was 1.70 mg/min for the three dosages studied. Davis and Westfall (20) found that the amount of unchanged salicylate excreted in dog urine was 38% while that of its metabolites was 62% of the total amount excreted. The salicylate metabolism rate, which was assumed to be 62% of the total excretion rate, was 1.05 mg/min for the three dosages investigated.

Viscera—The transient mass balance for the viscera body region (Vi) is:

$$\frac{d(V_{ViB,t}C_{T,ViB})}{dt} + \frac{d(V_{ViT}C_{T,ViT})}{dt} = Q_{Vi}(C_{T,B} - C_{T,ViB}) - R_r \quad \text{(Eq. 34)}$$

The renal excretion rate, R_r, of unchanged salicylate was 0.65 mg/min for the three dosages studied (10). The total salicylate concentration, $C_{T,ViB}$, and blood volume, $V_{ViB,t}$, in the viscera capillaries at time t may be written in a form similar to that for the liver capillaries. The permeability of the visceral (kidneys and heart) capillaries is assumed to be similar to that of the liver capillaries. Salicylate does not bind with the tissue components of the viscera either. Thus:

$$V_{ViT}C_{T,ViT} = (F_{w,ViT}V_{ViT})C_{F,ViT} = (F_{w,ViT}V_{ViT})C_{F,ViB} \quad \text{(Eq. 35)}$$

$$C_{T,ViB} = F_B(t)A + H_m(t)C_{F,ViB} \quad \text{(Eq. 36)}$$

and:

$$V_{ViB,t} = V_{ViB,0} + (Q_{SE} - Q_{BL})tF_{V,ViB} \quad \text{(Eq. 37)}$$

Substituting Eqs. 35–37 into Eq. 34 and rearranging yield:

$$\frac{dC_{F,ViB}}{dt} = [Q_{Vi}H_m(t)/L_{Vi}(t)]C_{F,B} - J_{Vi}(t)C_{F,ViB} - G_{Vi}(t) - R_r/L_{Vi}(t) \quad \text{(Eq. 38)}$$

where:

$$L_{Vi}(t) = V_{ViB,t}H_m(t) + V_{ViT}F_{w,ViT}$$

$$G_{Vi}(t) = A[V_{ViB,t}F_B'(t) + (Q_{SE} - Q_{BL})F_{V,ViB}F_B(t)]/L_{Vi}(t)$$

$$J_{Vi}(t) = [V_{ViB,t}H_m'(t) + (Q_{SE} - Q_{BL})F_{V,ViB}H_m(t) + Q_{Vi}H_m(t)]/L_{Vi}(t)$$

R_r = renal excretion rate of unchanged salicylate

GI Region—The transit mass balance for the GI region (GI) is:

$$\frac{d(V_{GIB,t}C_{T,GIB})}{dt} + \frac{d(V_{GIT}C_{T,GIT})}{dt} = Q_{GI}(C_{T,B} - C_{T,GIB}) \quad \text{(Eq. 39)}$$

where:

$$V_{GIT}C_{T,GIT} = (V_{GIT}F_{w,GIT})C_{F,GIT} = (V_{GIT}F_{w,GIT})C_{F,GIB} \quad \text{(Eq. 40)}$$

$$C_{T,GIB} = F_B(t)A + H_m(t)C_{F,GIB} \quad \text{(Eq. 41)}$$

and:

$$V_{GIB,t} = V_{GIB,0} + (Q_{SE} - Q_{BL})tF_{V,GIB} \quad \text{(Eq. 42)}$$

The following equation results from the substitution of Eqs. 40–42 into Eq. 39:

$$\frac{dC_{F,GIB}}{dt} = [Q_{GI}H_m(t)/L_{GI}(t)]C_{F,B} - J_{GI}(t)C_{F,GIB} - G_{GI}(t) \quad \text{(Eq. 43)}$$

where:

$$L_{GI}(t) = V_{GIB,t}H_m(t) + V_{GIT}F_{w,GIT}$$

$$G_{GI}(t) = A[V_{GIB,t}F_B'(t) + (Q_{SE} - Q_{BL})F_{V,GIB}F_B(t)]/L_{GI}(t)$$

$$J_{GI}(t) = [V_{GIB,t}H_m'(t) + (Q_{SE} - Q_{BL})F_{V,GIB}H_m(t) + Q_{GI}H_m(t)]/L_{GI}(t)$$

Adipose Tissue—The transit mass balance for the adipose tissue region (Ad) is:

$$\frac{d(V_{AdB,t}C_{T,AdB})}{dt} + \frac{d(V_{AdT}C_{T,AdT})}{dt} = Q_{Ad}(C_{T,B} - C_{T,AdB}) \quad \text{(Eq. 44)}$$

The tissue "binding" in adipose tissue is primarily due to the lipid solubility of the drug. Salicylate that is ionized at physiological pH is not lipid soluble. Salicylate in the small portion (about 19%) of water in adipose tissue accounts for the total amount of salicylate in the tissue portion, giving:

$$V_{AdT}C_{T,AdT} = (V_{AdT}F_{w,AdT})C_{F,AdT} = (V_{AdT}F_{w,AdT})C_{F,AdB} \quad \text{(Eq. 45)}$$

Also:

$$C_{T,AdB} = F_B(t)A + H_m(t)C_{F,AdB} \quad \text{(Eq. 46)}$$

and:

$$V_{AdB,t} = V_{AdB,0} + (Q_{SE} - Q_{BL})tF_{V,AdB} \quad \text{(Eq. 47)}$$

Substituting Eqs. 45–47 into Eq. 44 and rearranging yield:

$$\frac{dC_{F,AdB}}{dt} = [Q_{Ad}H_m(t)/L_{Ad}(t)]C_{F,B} - J_{Ad}(t)C_{F,AdB} - G_{Ad}(t) \quad \text{(Eq. 48)}$$

where:

$$L_{Ad}(t) = V_{AdB,t}H_m(t) + V_{AdT}F_{w,AdT}$$

$$G_{Ad}(t) = A[V_{AdB,t}F_B'(t) + (Q_{SE} - Q_{BL})F_{V,AdB}F_B(t)]/L_{Ad}(t)$$

$$J_{Ad}(t) = [V_{AdB,t}H_m'(t) + (Q_{SE} - Q_{BL})F_{V,AdB}H_m(t) + Q_{Ad}H_m(t)]/L_{Ad}(t)$$

Muscle—The transit mass balance for the muscle body region (Mu) is:

$$\frac{d(V_{MuB,t}C_{T,MuB})}{dt} + \frac{d(V_{MuT}C_{T,MuT})}{dt} = Q_{Mu}(C_{T,B} - C_{T,MuB}) \quad \text{(Eq. 49)}$$

Salicylate does not bind with the tissue components of muscle. Hence:

$$V_{MuT}C_{T,MuT} = (V_{MuT}F_{w,MuT})C_{F,MuT} \quad \text{(Eq. 50)}$$

$$C_{T,MuB} = F_B(t)A + H_m(t)C_{F,MuB} \quad \text{(Eq. 51)}$$

and:

$$V_{MuB,t} = V_{MuB,0} + (Q_{SE} - Q_{BL})tF_{V,MuB} \quad \text{(Eq. 52)}$$

It has been stated that the passage of water-soluble compounds such as salicylate through the muscle capillaries is restricted. The restricted drug transport can be described by:

$$\frac{dC_{F,MuT}}{dt} = P_{Mu}(C_{F,MuB} - C_{F,MuT}) \quad \text{(Eq. 53)}$$

Substituting Eqs. 50–53 into Eq. 49 and rearranging give:

$$\frac{dC_{F,MuB}}{dt} = (Q_{Mu}/V_{MuB,t})C_{F,B} - I_{Mu}(t)C_{F,MuB} + \{P_{Mu}V_{MuT}F_{w,MuT}/[V_{MuB,t}H_m(t)]\}C_{F,MuT} - S_{Mu}(t) \quad \text{(Eq. 54)}$$

where:

$$I_{Mu}(t) = [V_{MuB,t}H_m'(t) + (Q_{SE} - Q_{BL})F_{V,MuB}H_m(t) + P_{Mu}V_{MuT}F_{w,MuT} + Q_{Mu}H_m(t)]/[V_{MuB,t}H_m(t)]$$

$$S_{Mu}(t) = A\{F_B'(t)/H_m(t) + (Q_{SE} - Q_{BL})F_{V,MuB}F_B(t)/[V_{MuB,t}H_m(t)]\}$$

Brain—The transit mass balance for the brain region (Br) is

$$\frac{d(V_{BrB,t}C_{T,BrB})}{dt} + \frac{d(V_{BrT}C_{T,BrT})}{dt} = Q_{Br}(C_{T,B} - C_{T,BrB}) \quad \text{(Eq. 55)}$$

No binding between salicylate and the brain tissue was found (10). Hence:

$$V_{BrT}C_{T,BrT} = (V_{BrT}F_{w,BrT})C_{F,BrT} \quad \text{(Eq. 56)}$$

$$C_{T,BrB} = F_B(t)A + H_m(t)C_{F,BrB} \quad \text{(Eq. 57)}$$

and:

$$V_{BrB,t} = V_{BrB,0} + (Q_{SE} - Q_{BL})tF_{V,BrB} \quad \text{(Eq. 58)}$$

In the brain, the capillaries are much less permeable to water-soluble substances, perhaps because the endothelium of brain capillaries appears to be a continuous sheet of the glial connective tissue cells without visible pores (8). The cellular sheath of the brain capillaries highly impedes the passage of water-soluble compounds and accounts for the blood–brain barrier. The kinetics of salicylate penetration into cerebrospinal fluid and brain were studied previously (21, 22). The permeability constant, P_{CSF}, for salicylate penetration into cerebrospinal fluid (21, 22) is in the 0.0026–0.006-min^{-1} range. Materials diffuse relatively freely in either direction between the cerebrospinal fluid and extracellular fluid deep into brain tissue (23). Therefore, the value of the permeability constant for the blood–cerebrospinal fluid barrier may be adopted as that for the passage of the drug between the brain capillaries and the brain tissue, *i.e.*, $P_{Br} = P_{CSF}$.

The highly restricted transport of the drug in the brain can be written in terms of the free concentration difference between the capillaries and the brain tissue:

$$\frac{dC_{F,BrT}}{dt} = P_{Br}(C_{F,BrB} - C_{F,BrT}) \quad \text{(Eq. 59)}$$

Substituting Eqs. 56–59 into Eq. 55 and rearranging give:

$$\frac{dC_{F,BrB}}{dt} = (Q_{Br}/V_{BrB,t})C_{F,B} - I_{Br}(t)C_{F,BrB} + \{P_{Br}V_{BrT}F_{w,BrT}/[V_{BrB,t}H_m(t)]\}C_{F,BrT} - S_{Br}(t) \quad \text{(Eq. 60)}$$

where:

$$I_{Br}(t) = [V_{BrB,t}H_m'(t) + (Q_{SE} - Q_{BL})F_{V,BrB}H_m(t) + P_{Br}V_{BrT}F_{w,BrT} + Q_{Br}H_m(t)]/[V_{BrB,t}H_m(t)]$$

$$S_{Br}(t) = A\{F_B'(t)/H_m(t) + (Q_{SE} - Q_{BL})F_{V,BrB}F_B(t)/[V_{BrB,t}H_m(t)]\}$$

Kinetics of Salicylate Penetration into Cerebrospinal Fluid—In humans, the production rate of cerebrospinal fluid is in the 0.3–0.5-ml/min range with a total volume of about 120–200 ml (8, 23). The cerebrospinal fluid moves by bulk flow out of the ventricular system into the subarachnoid space and eventually returns to the bloodstream. The drug in the cerebrospinal fluid is removed as it returns to the general circulation.

The drug accumulation rate in the cerebrospinal fluid equals the drug penetration rate from the brain capillaries to the cerebrospinal fluid minus the drug removal rate due to the cerebrospinal fluid returning to the bloodstream. Thus:

$$\frac{d(V_{CSF}C_{CSF})}{dt} = V_{CSF}P_{CSF}(C_{F,BrB} - C_{CSF}) - Q_{CSF}C_{CSF} \quad \text{(Eq. 61)}$$

Equation 61 may be simplified to:

$$\frac{dC_{CSF}}{dt} = P_{CSF}(C_{F,BrB} - C_{CSF}) - (Q_{CSF}/V_{CSF})C_{CSF} \quad \text{(Eq. 62)}$$

where $C_{F,BrB}$ and C_{CSF} are the free concentrations in the brain capillaries and in the cerebrospinal fluid, respectively; P_{CSF} is the permeability constant for drug passage into the cerebrospinal fluid; Q_{CSF} is the production or removal rate of the cerebrospinal fluid; and V_{CSF} is the total cerebrospinal fluid volume.

There are 10 unknown variables (seven free concentrations in the blood pool and in the capillaries of the other six body regions plus three free concentrations in the cerebrospinal fluid and in the tissue portions of brain and muscle) in a system of 10 simultaneous equations (Eqs. 24, 32, 38, 43, 48, 53, 54, 59, 60, and 62). Ten equations can serve to solve 10 variables. Therefore, a system of the 10 simultaneous first-order ordinary differential equations can be solved numerically. In this study, the Runge-Kutta fourth-order method (10, 24) for solution of ordinary differential equations was employed to solve the 10 simultaneous equations. The solution gives simultaneously the kinetics of the 10 variables (free salicylate concentrations in this case).

Since the total salicylate concentration, $C_{T,B}$, in the blood pool and both the total salicylate concentration, $C_{T,YzB}$, in the capillary blood and the total salicylate concentration, $C_{T,YzT}$, in the tissue portion of any body region, Yz, can be correlated with their corresponding free salicylate concentrations by Eqs. 21, 22, 29, 35, 40, 45, 50, and 56, all kinetics of total salicylate concentrations in the blood pool and in both the capillary blood and tissue portions of various body regions can also be determined by the model. Model feasibility can be demonstrated by comparing the experimental kinetic data with the model-predicted results. Since the experimentally determined salicylate concentration in any organ, Yz, represents the total salicylate concentration, $C_{T,Yz}$, in that organ, which can be calculated in terms of the total salicylate concentration, $C_{T,YzB}$, in the capillary blood and the total salicylate concentration $C_{T,YzT}$, in the tissue portion of the body region by the following equation:

$$C_{T,Yz}(V_{YzB} + V_{YzT}) = C_{T,YzB}V_{YzB} + C_{T,YzT}V_{YzT} \quad \text{(Eq. 63)}$$

the pharmacokinetics of total salicylate levels in various organs and tissues can be predicted by the model.

During the 6-hr experiment, blood loss occurred due to the bleeding from taking various tissue samples to obtain experimental kinetic data. Normal saline was continuously supplied to maintain adequate blood pressure and blood volume. The factors accounting for the blood dilution and the drug loss accompanying blood loss were considered in constructing the pharmacokinetic model. However, the kinetic behavior of salicylate distribution in the body of an intact dog in which tissue samples are not taken is expected to be a little different from that in the dog from which various tissue samples are taken. When tissue samples are not taken, neither blood loss nor blood dilution occurs. The fraction of whole (nondiluted) blood, $F_B(t)$, is always one, and the rates of saline supply and blood loss are zero. The solution to a system of the 10 simultaneous differential equations will give slightly higher salicylate levels in the body because there is no drug loss accompanying blood loss.

Effect of Hemoperfusion on Salicylate Kinetics—The effectiveness of hemoperfusion using albumin-coated activated carbon for acute, severely intoxicated cases was evaluated in terms of its effect on the salicylate body distribution (10). It was also attempted to apply the model to predict the salicylate pharmacokinetics in the body due to the extracorporeal treatment. A blood pump was used to shunt part of the femoral arterial blood through the extracorporeal device, and the "clean" blood out of the device was conducted into the femoral vein during the treatment. Thus:

$$Q_{Mu,ET} = Q_{Mu} - Q_{ET} \quad \text{(Eq. 64)}$$

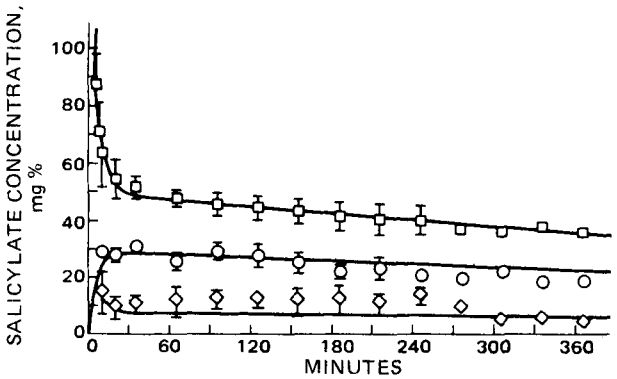


Figure 1—*Predicted (solid lines) and experimental salicylate concentrations in blood (□), muscle (○), and adipose tissue (◇) at a dose of 285 mg/kg (sodium salicylate).*

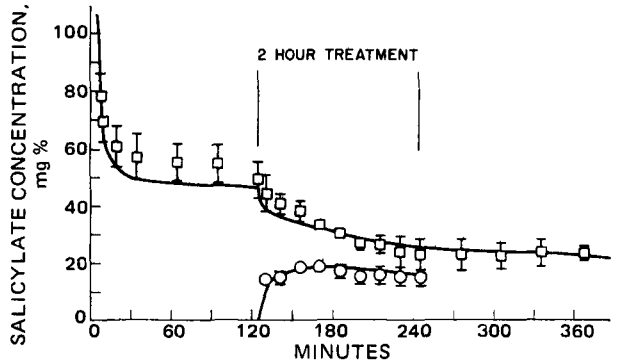


Figure 3—*Predicted (solid lines) and experimental salicylate concentrations in blood under the influence of 2-hr hemoperfusion treatment at a dose of 285 mg/kg. Key: □, inflow blood; and ○, outflow blood.*

where $Q_{Mu,ET}$ is the blood flow rate through the muscle during the extracorporeal treatment, Q_{ET} is the blood perfusion rate shunted through the extracorporeal device, and Q_{Mu} is the blood flow rate through the muscle without shunting blood through the device.

The salicylate removal rate by the extracorporeal treatment, R_{ET}, can be calculated by:

$$R_{ET} = Q_{ET}(C_{T,B} - C_{T,B,\text{out}}) \quad \text{(Eq. 65)}$$

where $C_{T,B}$ is the total drug concentration from the blood pool entering the extracorporeal device and $C_{T,B,\text{out}}$ is the total drug concentration in the outflow blood from the device.

During extracorporeal treatment, Eqs. 13 and 49 of transient mass balance for the blood pool and for the muscle region should be modified to:

$$\frac{d(V_{B,t}C_{T,B})}{dt} = (Q_{Br}C_{T,BrB} + Q_{Li}C_{T,LiB} + Q_{Vi}C_{T,ViB} + Q_{Mu,ET}C_{T,MuB} + Q_{ET}C_{T,B,\text{out}} + Q_{Ad}C_{T,AdB}) + Mg(t) - Q_BC_{T,B} \quad \text{(Eq. 66)}$$

and:

$$\frac{d(V_{MuB,t}C_{T,MuB})}{dt} + \frac{d(V_{MuT}C_{T,MuT})}{dt} = Q_{Mu,ET}(C_{T,B} - C_{T,MuB}) \quad \text{(Eq. 67)}$$

The right-hand side of Eq. 66 can also be written in terms of the salicylate removal rate by the extracorporeal treatment, R_{ET}, from Eq. 65 and becomes:

$$\frac{d(V_{B,t}C_{T,B})}{dt} = (Q_{Br}C_{T,BrB} + Q_{Li}C_{T,LiB} + Q_{Vi}C_{T,ViB} + Q_{Mu,ET}C_{T,MuB} + Q_{Ad}C_{T,AdB}) + Mg(t) - (Q_B - Q_{ET})C_{T,B} - R_{ET} \quad \text{(Eq. 68)}$$

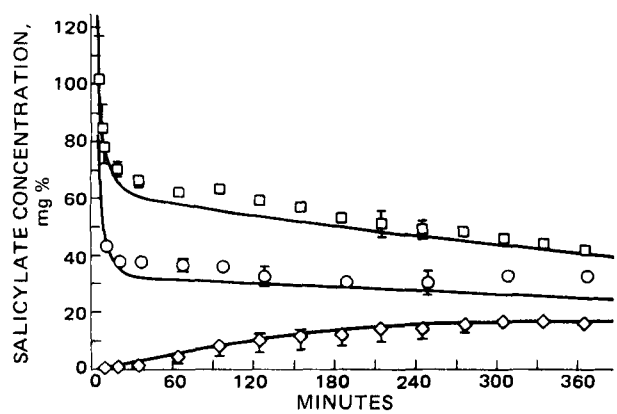


Figure 2—*Predicted (solid lines) and experimental salicylate concentrations in plasma (□), liver (○), and cerebrospinal fluid (◇) at a dose of 285 mg/kg (sodium salicylate).*

Therefore, the pharmacokinetic behavior of salicylate in the body during the extracorporeal treatment also can be predicted by solving a system of 10 simultaneous equations.

RESULTS AND DISCUSSION

The values of parameters and constants necessary for solving the system of 10 simultaneous differential equations are shown in Table I and Scheme I.

Three different dosages of sodium salicylate were used: 135 mg/kg (therapeutic), 210 mg/kg (moderate intoxication), and 285 mg/kg (severe intoxication). Only the 285-mg/kg data are given here; data for the other dosages are available, however (10). Three or four mongrel dogs (15–25 kg) were evaluated with each dosage. An infusion pump was employed to infuse each dose at a constant rate over 5 min. A detailed description of the experimental method for quantitative studies on salicylate kinetics in cerebrospinal fluid, blood, plasma, liver, muscle, and adipose tissue is available (10).

The mean values ($\pm SD$) of the experimentally determined salicylate concentrations with time and the predicted pharmacokinetics (solid lines) by the model are shown in Figs. 1 and 2 for the 285-mg/kg dose. If a calculated standard deviation is within the size of a symbol representing a mean value, then the standard deviation is not shown in the figures. Time zero in the figures is the time just prior to infusing a dose. The good agreement between predicted kinetics and experimental data demonstrates model feasibility.

In an experiment with hemoperfusion treatment, a severely intoxicating dose (285 mg/kg) of sodium salicylate was administered intravenously to dogs (19–26 kg, average 23 kg) at a constant rate for 5 min. Two hours later, the poisoned dog was treated by an extracorporeal device containing 250 g (wet weight) of albumin-coated activated carbon[1] for 2 hr (10). The arterial blood from the femoral artery was shunted through the extracorporeal cartridge; salicylate in the blood was adsorbed by the carbon, and the outflow "clean" blood returned to the femoral vein.

The salicylate removal rate by hemoperfusion was calculated, as stated previously, in terms of the blood perfusion rate and the concentration difference between inflow and outflow blood samples (Fig. 3). The blood perfusion rate shunted from the femoral artery of a 23-kg (average) dog in the experiment (10) was kept at 100 ml/min by a blood pump. However, the physiological parameters employed in the pharmacokinetic modeling are based on a 15-kg (average) dog. Hence, the blood perfusion rate used in this model was adjusted to that for a 15-kg dog and gave 65 ml/min as the result of multiplying a ratio of the two body weights.

Figures 4–6 show the experimental kinetic data of salicylate levels (mean value ± SD) in blood, plasma, muscle, adipose tissue, and cerebrospinal fluid and the predicted kinetics (solid lines) by the model under the effect of the 2-hr treatment. The kinetic changes of salicylate levels in the body during and after the hemoperfusion are also well predicted by the model with certain modifications in blood flows and in equations as expressed in the previous section.

The pharmacological effect of a drug is generally reflected better by the free (unbound) drug levels in blood or target organ(s). The relationships between free and total drug concentrations in blood and various

[1] Witco 517, Witco Chemical Co.

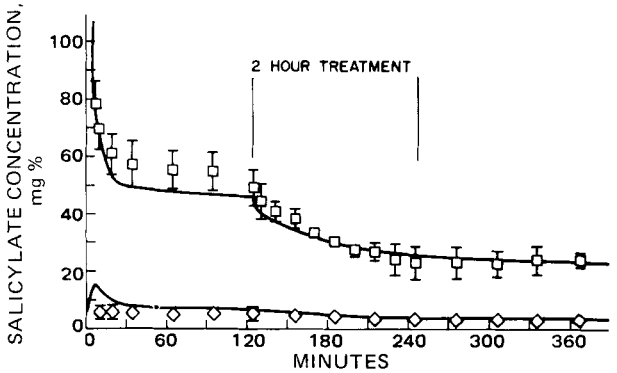


Figure 4—*Predicted (solid lines) and experimental salicylate concentrations in blood (□) and adipose tissue (◇) under the influence of 2-hr hemoperfusion treatment at a dose of 285 mg/kg.*

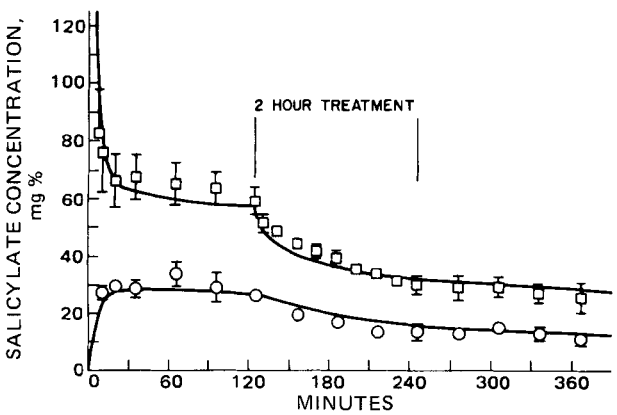


Figure 5—*Predicted (solid lines) and experimental salicylate concentrations in plasma (□) and muscle (○) under the influence of 2-hr hemoperfusion treatment at a dose of 285 mg/kg.*

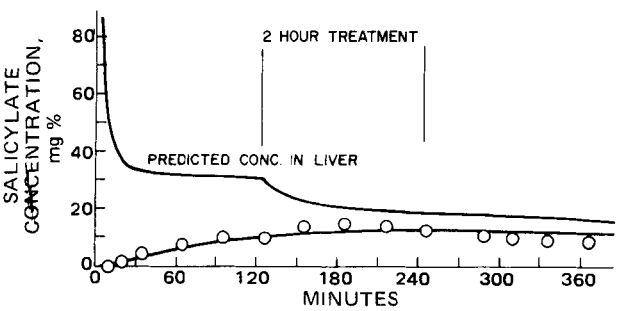


Figure 6—*Predicted (solid lines) and experimental salicylate concentrations in cerebrospinal fluid (○) and liver under the influence of 2-hr hemoperfusion treatment at a dose of 285 mg/kg. No experimental data were obtained for liver as a result of heparin therapy being applied to the dog with the hemoperfusion treatment (10).*

tissues were considered in constructing the equations for the model. Figures 7 and 8 show experimental (mean value ± *SD*) and predicted (solid lines) kinetics of free and total salicylate levels in plasma with and without the hemoperfusion treatment. The results predicted by the model agree with the experimental data.

Curves and data comparable to those reported in Figs. 1–8 are also available for the 135- and 210-mg/kg doses (10).

CONCLUSIONS

Since knowledge of the kinetic behavior of a drug in blood or plasma may not provide sufficient information for appropriate therapy, kinetic information of drug levels in brain, cerebrospinal fluid, blood, organs, and tissues of pharmacological interest may be necessary for the development of improved dosage regimens. The pharmacokinetic model

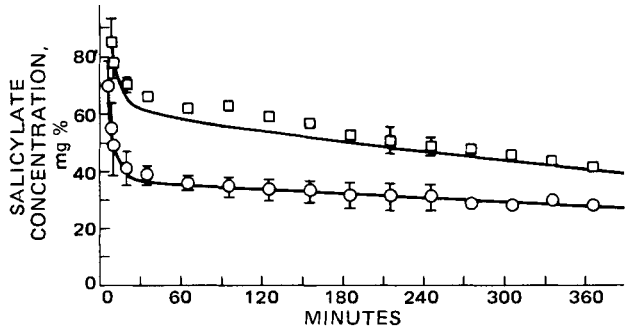


Figure 7—*Predicted (solid lines) and experimental free salicylate concentration (○) and total salicylate concentration (□) in plasma at a dose of 285 mg/kg (sodium salicylate).*

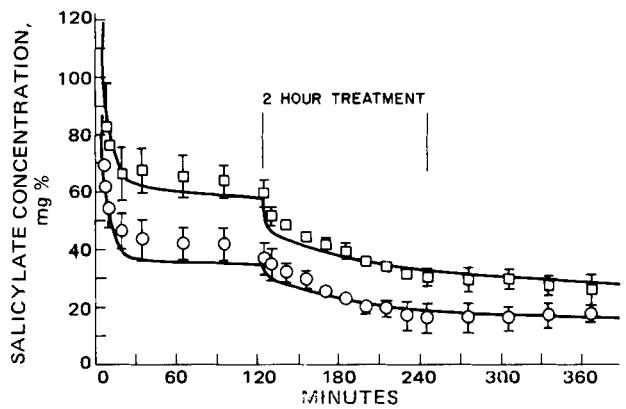


Figure 8—*Predicted (solid lines) and experimental free salicylate concentration (○) and total salicylate concentration (□) in plasma under the influence of 2-hr hemoperfusion treatment at a dose of 285 mg/kg.*

presented in this study can predict salicylate levels not only in blood or plasma but also in cerebrospinal fluid, liver, and other tissues. Conventional compartment models are unable to do so.

Free drug concentrations (variables to be solved) in all body regions (Scheme I) are involved in Eq. 24 while the free drug concentration in the blood pool appears in the equation for each body region. Thus, each equation in a system of simultaneous differential equations is not independent but interrelated to the others. This feature of the model has an important application in clinical pharmacokinetics. If the model for a given drug can be verified in a species pharmacokinetically similar to humans, then it can be applied to predict pharmacokinetics of the drug in human blood, organs, and tissues of pharmacological importance by using the physiological and biochemical parameters of humans.

The experimentally observed kinetics of drug levels in blood or plasma may be used to compare with the corresponding kinetics predicted by the model. If they agree well, the model-predicted kinetics of drug distribution in the other body regions that are difficult to sample may be expected to represent closely the actual kinetic courses because of the interrelated characteristics of the equations. Therefore, the model can furnish more complete and valuable information for optimal therapeutic regimens. The model has been successfully applied to predict the pharmacokinetics of salicylate in the dog with and without extracorporeal activated carbon treatment.

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Frequency Distribution of Bilirubin Intrinsic Clearance in Adult Male Sprague–Dawley Rats

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Abstract □ The intrinsic body clearance of bilirubin was determined in 48 adult male Sprague–Dawley rats that received an intravenous infusion of bilirubin. The intrinsic body clearance was calculated from the infusion rate, the steady-state plasma concentration of total (free and protein-bound) bilirubin, and the free fraction of bilirubin in plasma. The intrinsic body clearance of bilirubin ranged from 5.05 to 13.20 liters/kg/min and was bimodally distributed, with half of the animals in each group. The plasma free fraction of bilirubin ranged from 0.00025 to 0.00077 (mean 0.00053) in the 24 intrinsically rapid metabolizers of bilirubin and from 0.00048 to 0.00103 (mean 0.00075) in the intrinsically slow metabolizers of the pigment. Thus, interindividual differences in the *total* clearance of bilirubin in the rats are due to differences in both intrinsic body clearance and plasma protein binding.

Keyphrases □ Bilirubin—intrinsic body clearance, frequency distribution, rats □ Clearance, intrinsic body—bilirubin, frequency distribution, rats □ Pigments—bilirubin, intrinsic body clearance, frequency distribution, rats

The heme pigment bilirubin is eliminated in humans and animals almost entirely by conjugative pathways (1). The concentration of bilirubin in plasma is a frequently used diagnostic index because it reflects changes in the formation and elimination rates of the pigment that may be caused by hemolysis, liver disease, and other pathologic conditions.

Preliminary studies on a small group of rats revealed pronounced interindividual differences in the total body clearance of bilirubin which could be ascribed largely to corresponding differences in the plasma protein binding of the pigment (2). This study has been extended to a total of 48 animals to determine the magnitude of interindividual differences in total body clearance, intrinsic clearance, and plasma free fraction of bilirubin.

EXPERIMENTAL

Forty-eight male Sprague–Dawley rats[1], 300–400 g, were maintained on a standard diet[2] and received an infusion of bilirubin into the right jugular vein. Forty animals received bilirubin at a rate of 0.8 mg/kg/min for 15 min and then 0.32 mg/kg/min for up to 4 hr; the other eight rats were infused at a rate of 0.8 mg/kg/min for the entire period (except for three of these animals that received 2 mg/kg/min for the first 15 min). Blood samples were obtained periodically, and plasma was assayed for free (3) and total (4) unconjugated bilirubin.

Steady-state conditions were ascertained as previously described (2). The total body clearance of bilirubin was calculated by dividing the maintenance infusion rate by the steady-state concentration of total bilirubin in plasma. The intrinsic body clearance was determined (5) by dividing the total body clearance by the free fraction of bilirubin in plasma (free fraction = free ÷ total concentration of bilirubin). These experiments were carried out over 2 years, 1–4 weeks after receipt of the animals.

Histograms to describe the frequency distribution of intrinsic clearance and log intrinsic clearance values were constructed by iteratively changing the class interval to maximize the number of bars in the respective graph while minimizing the number of regional reversals (modes and antimodes), as suggested by Martin *et al.* (6). For the bimodal characterization, the mean value, standard deviation, and fraction of the total population in each Gaussian component were estimated (7) by dividing the appropriate histogram at the antimode and considering each segment of the population as a separate Gaussian or log-normally distributed component.

[1] Blue Spruce Farms, Altamont, N.Y.
[2] Charles River Formula 4RF.