Hydrodynamic Analog Model for Pharmacokinetics I: Model and Its Usefulness

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Abstract □ A novel hydrodynamic model for drug distribution, when the drug is administered intravenously in physiological systems, is presented. In addition to obtaining results of familiar multicompartment models, the theory presents fresh insights into pharmacokinetic problems. A detailed procedure is included for evaluating drug–physiological system parameters such as the elimination rate constant, volumes of distribution, and permeability properties from the experimental time course of concentration of the central compartment.

Keyphrases □ Model, hydrodynamic analog—proposed for pharmacokinetics, applications, equations □ *Diffusion model*, hydrodynamic, analog—proposed for pharmacokinetics, applications, equations □ Pharmacokinetics—hydrodynamic analog model proposed, evaluation of elimination rate constant, volume of distribution, and permeability properties

Several examples of experimental studies of drug elimination from plasma following absorption and initial distribution are available (1–4). Intravenous administration of a drug assures that the administered substance is initially distributed in plasma and then to other tissues including the kidneys, and finally it is eliminated from the body. The salient feature of these studies is that variations of drug concentration in plasma with time can be adequately represented as the sum of two or three exponential functions, the characteristic parameters of which are evaluated experimentally.

The theoretical foundations of such pharmacokinetic experiments are based on the two- and three-compartment models (1, 2). This report presents a novel hydrodynamic picture of what is probably happening to substances administered intravenously (5). The model presented is simplified for clarity and can possibly account for many experimental observations, including the kink observed in the plot of plasma concentration of dicumarol (4) *versus* time.

The model presented enables one to relate the kinetic parameters of familiar compartment models with physical parameters such as the permeability of barriers separating the compartments. The model can be improved by inclusion of appropriate chemical reactions with which the drug can participate in certain compartments and may help in quantitizing phenomena such as bone growth in physiology. Of immediate interest is that the model sheds new light on certain aspects of existing compartment model theories.

HYDRODYNAMIC ANALOG OF THREE-COMPARTMENT MODEL ANALYSIS

Consider the flow of a liquid into Compartments 2 and 3 from Compartment 1 and to the outside through a tap connected to Compartment 2 (Fig. 1). Assume that at time $t = 0$, the liquid is poured into Compartment 1, with no liquid present in Compartments 2 and 3. The partition between Compartments 1 and 3 is porous and has an effective pore area, A_{13}, and thickness, h_{13}. Similarly, the partition between Compartments 1 and 2 is also porous, with an effective pore area, A_{12}, and thickness, h_{12}.

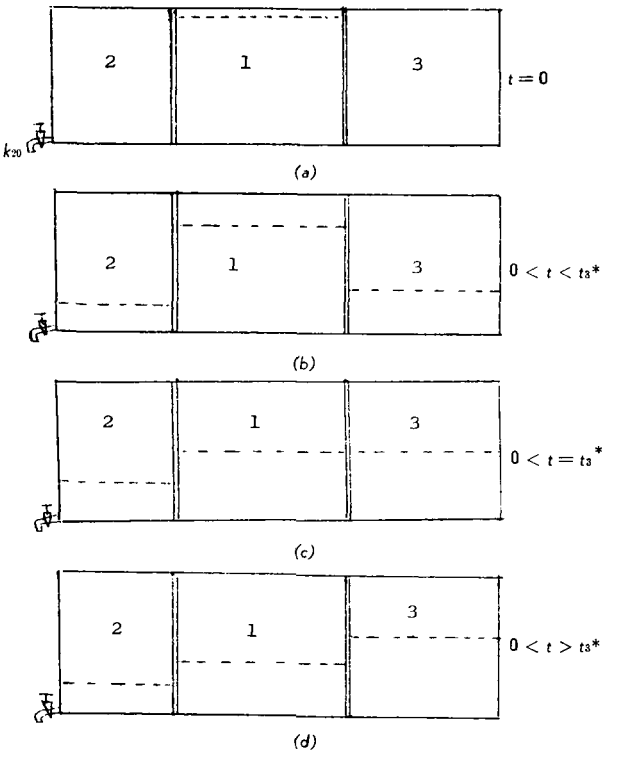

Figure 1—*Hydrodynamic analogy of the three-compartment system.*

Then study the levels of liquid in the three compartments at four arbitrary times (Fig. 1). Initially the liquid flows from Compartment 1 to Compartments 2 and 3 at different rates, depending on the porosity of partitions and the volumes of compartments. This results in a rise of the levels of liquid in Compartments 2 and 3 and a corresponding decrease in the level of liquid in Compartment 1. As time progresses, the difference in levels between Compartments 1 and 3 decreases and the levels in Compartments 1 and 3 become equal at a certain time, $t = t_3^*$. At this time, the net flow of liquid between Compartments 1 and 3 vanishes.

If the tap connected to Compartment 2 has been closed all of the time, there will come a time, $t = t^0$, when levels in all three compartments become equal and the net flow between compartments vanishes. (Discussion about whether t^0 is finite or infinite is subtle and not very relevant to the present discussion.) This represents the most stable equilibrium state of the system. Since, however, the tap connected to Compartment 2 is always (slightly) open, this equilibrium state is never reached in the system depicted in Fig. 1 for reasonable times. The stable state is when all of the liquid in the three compartments has drained to the outside. Thus, for times greater than t_3^*, the direction of flow of liquid between Compartments 1 and 3 reverses and the levels of liquids in the three compartments attain the configuration depicted in Fig. 1*d*. Flow to the outside through the tap continues until all of the liquid is depleted.

The multicompartment models of pharmacokinetics can now be studied with the help of this hydrodynamic analogy, where levels

are to be replaced by concentrations. Certain conclusions of a general nature can be obtained from this extremely simple example.

First, net loss of material from the system occurs through the elimination process (*i.e.*, leak through the tap ignoring any metabolic process loss in compartments), which may be adequately represented by a first-order rate constant, k_{20}. Thus, one has the mass conservation equation for the three-compartment model:

$$(d/dt)\{X_1(t)V_1 + X_2(t)V_2 + X_3(t)V_3\} = -k_{20}V_2X_2(t) \quad \text{(Eq. 1)}$$

where $X_1(t)$, $X_2(t)$, and $X_3(t)$ are concentrations in Compartments 1, 2, and 3, respectively, at time t; and V_1, V_2, and V_3 are the volumes of distribution of the material in Compartments 1, 2, and 3, respectively. The rate of loss of material from the system at time t is assumed to be proportional to the concentration in Compartment 2 at time t, the negative sign in Eq. 1 denoting the loss.

If $Q_{12}(t)$ and $Q_{13}(t)$ represent the net (total) amount of substance transferred from Compartment 1 to Compartments 2 and 3, respectively, from time zero to time t, the mass balance equation may be written as (6):

$$\dot{X}_1(t) + \dot{X}_2(t) + \dot{X}_3(t) = +\dot{Q}_{12}\{(V_1 - V_2)/V_1V_2\} + \dot{Q}_{13}\{(V_1 - V_3)/V_1V_3\} - k_{20}X_2(t) \quad \text{(Eq. 2)}$$

where the super dots indicate first time derivatives of appropriate quantities.

Only when the volumes of distribution of the three compartments equal one another does one get a relation of the type (7):

$$\dot{X}_1(t) + \dot{X}_2(t) + \dot{X}_3(t) = -k_{20}X_2(t) \quad \text{(Eq. 3)}$$

Second, the appropriate initial conditions are that at time $t = 0$, one has:

$$X_1(0) = \text{dose}/V_1 \quad \text{(Eq. 4}a\text{)}$$
$$X_2(0) = X_3(0) = 0 \quad \text{(Eq. 4}b\text{)}$$

The third conclusion that one arrives at is that the transport from Compartment 1 to 3 occurs only in one direction at any time t; the direction of transport is determined by the difference in concentrations between Compartments 1 and 3. Fourth, there exists a positive definite critical time t_3^*, at which the flow between Compartments 1 and 3 vanishes. For times greater than t_3^*, the loss in concentration in Compartment 1 due to the flow to Compartment 2 and the outside is partly offset by the flow of material from Compartment 3 to 1.

The fifth conclusion is that if the leak to the outside is eliminated, *i.e.*, the tap is closed at all times, it takes a minimum finite time, t^0, for the system to reach equilibrium when concentrations in the three compartments will be equal. When k_{20} is equal to zero, only for times equal to and greater than t^0, the right-hand side of Eq. 3 vanishes and Eq. 3 is valid with unequal volumes of distribution of compartments.

Finally, the sixth conclusion that one arrives at from the simple hydrodynamic model is that the variation in concentrations of compartments with respect to time for the system is determined by the set of differential equations:

$$\dot{X}_1(t) = -\{(\delta_{12} + \delta_{13})/V_1\}X_1 + (\delta_{12}/V_1)X_2 + (\delta_{13}/V_1)X_3 \quad \text{(Eq. 5}a\text{)}$$
$$\dot{X}_2(t) = -\{(\delta_{12}/V_2) + k_{20}\}X_2 + (\delta_{12}/V_2)X_1 \quad \text{(Eq. 5}b\text{)}$$
$$\dot{X}_3(t) = -(\delta_{13}/V_3)X_3 + (\delta_{13}/V_3)X_1 \quad \text{(Eq. 5}c\text{)}$$

The constant parameters δ_{12} and δ_{13} can be identified with the use of Fick's law (8) as:

$$\delta_{12} = (D_{12}A_{12}/h_{12}) \quad \text{(Eq. 6}a\text{)}$$
$$\delta_{13} = (D_{13}A_{13}/h_{13}) \quad \text{(Eq. 6}b\text{)}$$

where D_{12} and D_{13} are the diffusion coefficients of administered substance in the barrier between Compartments 1 and 2 and Compartments 1 and 3, respectively; A_{12} and h_{12} are the effective pore area and thickness, respectively, of the barrier separating Compartments 1 and 2; and A_{13} and h_{13} are the effective pore area and thickness, respectively, of the barrier separating Compartments 1 and 3.

The differential equations of conventional pharmacokinetics deal in amounts rather than in concentrations. With the identifications:

$$k_{12} = (\delta_{12}/V_1) \quad k_{21} = (\delta_{12}/V_2) \quad \text{(Eq. 7}a\text{)}$$
$$k_{13} = (\delta_{13}/V_1) \quad k_{31} = (\delta_{13}/V_3) \quad \text{(Eq. 7}b\text{)}$$

where k_{12}, k_{21}, k_{13}, and k_{31} are the first-order rate constants of the familiar three-compartment model, one obtains a one-to-one correspondence between the hydrodynamic analog and the familiar pharmacokinetic expressions.

It is a necessary consequence of the hydrodynamic analogy model and principles of irreversible thermodynamics that:

$$k_{12}^*V_1 = k_{21}^*V_2 \quad \text{(Eq. 8}a\text{)}$$
$$k_{13}^*V_1 = k_{31}^*V_3 \quad \text{(Eq. 8}b\text{)}$$

Thus, with the hydrodynamic model, one is able to relate diffusion coefficients in the barrier, effective pore area, and permeability of the substances across the barrier with the kinetic first-order rate coefficients of the familiar compartmental model equations.

THEORETICAL

Based on the assumption that the rate of transfer of solute material between adjacent compartments at any time t is proportional to the difference in concentrations between the compartments at time t, one has the set of coupled differential equations:

$$\dot{Q}_{12}(t) = \delta_{12}[X_1(t) - X_2(t)] \quad \text{(Eq. 9}a\text{)}$$
$$\dot{Q}_{13}(t) = \delta_{13}[X_1(t) - X_3(t)] \quad \text{(Eq. 9}b\text{)}$$

where $\dot{Q}_{12}(t)$ is the rate of transfer of solute from Compartment 1 to 2 at time t. The concentrations of drug substance in Compartments 1 and 3 at any time t are related to $Q_{12}(t)$ and $Q_{13}(t)$ by the relations (6, 8):

$$X_1(t) = (\text{dose}/V_1) - (1/V_1)\{Q_{12}(t) + Q_{13}(t)\} \quad \text{(Eq. 10}a\text{)}$$
$$X_3(t) = Q_{13}(t)/V_3 \quad \text{(Eq. 10}b\text{)}$$

With k_{20} nonvanishing, the concentration in Compartment 2 at time t is related to $Q_{12}(t)$ by the differential equation:

$$\dot{X}_2(t) + k_{20}X_2(t) = \dot{Q}_{12}(t)/V_2 \quad \text{(Eq. 11)}$$

To obtain the solutions of Eqs. 9*a* and 9*b* subject to the constraints of Eqs. 10*a*, 10*b*, and 11, it is convenient to differentiate once more with respect to time:

$$\ddot{Q}_{12}(t) = \delta_{12}[\dot{X}_1 - \dot{X}_2] \quad \text{(Eq. 12}a\text{)}$$
$$\ddot{Q}_{13}(t) = \delta_{13}[\dot{X}_1 - \dot{X}_3] \quad \text{(Eq. 12}b\text{)}$$

Since the solution of Eq. 11 is evident with vanishing $\dot{Q}_{12}$, assume that the solution of Eqs. 12*a* and 12*b* is given by:

$$X_2(t) = A(t)\exp(-k_{20}t) \quad \text{(Eq. 13)}$$

where $A(t)$ is an unknown function of t to be determined. Use of Eqs. 10*a*, 10*b*, 11, and 13 in Eqs. 12*a* and 12*b* yields, upon rearrangement:

$$\dot{Q}_{12}(t) = \dot{A}(t)V_2\exp(-k_{20}t) \quad \text{(Eq. 14}a\text{)}$$
$$\dot{Q}_{13}(t) = -(V_1V_2/\delta_{12})\{\exp(-k_{20}t)[\ddot{A} + \dot{A}(\alpha_{12} - k_{20}) - A(k_{20}\delta_{12}/V_2)] \quad \text{(Eq. 14}b\text{)}$$
$$\alpha_{12} = \delta_{12}(V_1 + V_2)/V_1V_2 \quad \text{(Eq. 14}c\text{)}$$

Substitution of the results of Eqs. 14*a*–14*c* in Eqs. 15*a* and 15*b* obtainable from Eq. 12*b*—*viz.*:

$$\dddot{Q}_{13} + \alpha_{13}\ddot{Q}_{13} = -(\delta_{13}/V_1)\dot{Q}_{12}(t) \quad \text{(Eq. 15}a\text{)}$$
$$\alpha_{13} = \delta_{13}(V_1 + V_3)/V_1V_3 \quad \text{(Eq. 15}b\text{)}$$

yields a third-order differential equation for the function $A(t)$ with constant coefficients as:

$$\dddot{A} + \ddot{A}P + \dot{A}Q + AR = 0 \qquad \text{(Eq. 16)}$$

where P, Q, and R are time-independent parameters related to the permeabilities, volumes of compartments, and k_{20} by:

$$P = \alpha_{12} + \alpha_{13} - 2k_{20} \qquad \text{(Eq. 17a)}$$

$$Q = [k_{20}\{k_{20} - (\delta_{12}/V_2) - \alpha_{12} - \alpha_{13}\} + \alpha_{12}\alpha_{13} - (\delta_{12}\delta_{13}/V_1^2)] \qquad \text{(Eq. 17b)}$$

$$R = k_{20}(\delta_{12}/V_2)[k_{20} - \alpha_{13}] \qquad \text{(Eq. 17c)}$$

Evidently, the solution of the differential Eq. 16 is:

$$A(t) = \sum_{\sigma=1}^{3} C_\sigma \exp(r_\sigma t) \qquad \text{(Eq. 18)}$$

where C_σ (σ = 1, 2, 3) are constants of integration to be determined from boundary conditions, and r_σ (σ = 1, 2, 3) are the three roots of the cubic equation:

$$r^3 + r^2P + rQ + R = 0 \qquad \text{(Eq. 19)}$$

TIME DEPENDENCE OF CONCENTRATIONS IN COMPARTMENTS

From the results of the previous section, one is now in a position to write down the expressions for time dependence of concentrations in the three compartments:

$$X_1(t) = \sum_\sigma C_\sigma\{1 + mr_\sigma\} \exp(\mu_\sigma t) \qquad \text{(Eq. 20a)}$$

$$X_2(t) = \sum_\sigma C_\sigma \exp(\mu_\sigma t) \qquad \text{(Eq. 20b)}$$

$$X_3(t) = \sum_\sigma C_\sigma \exp(\mu_\sigma t)[1 + r_\sigma m + (V_1V_2/\delta_{12}\delta_{13})M_\sigma] \qquad \text{(Eq. 20c)}$$

$$M_\sigma = r_\sigma^2 + r_\sigma(\alpha_{12} - k_{20}) - k_{20}(\delta_{12}/V_2) \qquad \text{(Eq. 20d)}$$

$$\mu_\sigma = r_\sigma - k_{20} \text{ and } m = (V_2/\delta_{12}) \qquad \text{(Eq. 20e)}$$

Utilizing the initial conditions that at time $t = 0$ the concentrations in Compartments 2 and 3 are null and that the concentration in Compartment 1 equals (dose/V_1), one has from Eqs. 20a–20e:

$$\sum_{\sigma=1}^{3} C_\sigma r_\sigma = \eta \qquad \text{(Eq. 21a)}$$

$$\sum_{\sigma=1}^{3} C_\sigma = 0 \qquad \text{(Eq. 21b)}$$

$$\sum_{\sigma=1}^{3} C_\sigma r_\sigma^2 = \eta\omega \qquad \text{(Eq. 21c)}$$

$$\omega = k_{20} - \alpha_{12} - (\delta_{13}/V_1) \qquad \text{(Eq. 21d)}$$

$$\eta = \text{dose}(\delta_{12}/V_1V_2) \qquad \text{(Eq. 21e)}$$

Solving the set of simultaneous Eqs. 21a–21c, one has the expressions for the three integration constants for the three-compartment model:

$$C_1 = \eta(\omega - r_2 - r_3)/\{(r_1 - r_3)(r_1 - r_2)\} \qquad \text{(Eq. 22a)}$$

$$C_2 = \eta(r_1 + r_3 - \omega)/\{(r_1 - r_2)(r_2 - r_3)\} \qquad \text{(Eq. 22b)}$$

$$C_3 = \eta(\omega - r_1 - r_2)/\{(r_1 - r_3)(r_2 - r_3)\} \qquad \text{(Eq. 22c)}$$

Thus, one has the result that all integration constants are proportional to dose and one can define a parameter p such that:

$$C_2 = C_1p \qquad \text{(Eq. 23a)}$$

$$C_3 = -(1 + p)C_1 \qquad \text{(Eq. 23b)}$$

$$p = [(r_1 + r_3 - \omega) \times (r_1 - r_3)]/[(\omega - r_2 - r_3)(r_2 - r_3)] \qquad \text{(Eq. 23c)}$$

The parameter p is characteristic of the three-compartment pharmacokinetic system. The salient point is that even though the results of this analysis in Eqs. 20a–20e resemble the results of the familiar three-compartment model, as the sum of three exponential terms, one of the integration constants must have a sign opposite to the signs of other two integration constants. This result has the implication (which is not generally recognized) that a *function of the type* $\sum_\sigma A_\sigma \exp(\mu_\sigma t)$, *where* A_σ*'s are constants and* μ_σ*'s are negative definite time-independent quantities, can have extremum values.* This aspect is utilized to explain (9) the observed kink in the plot of plasma concentration *versus* time[1].

EVALUATION OF SYSTEM PARAMETERS FROM EXPERIMENTAL DATA

Aside from the profferred explanation for the possible existence and observation of kinks in the plot of the concentration of the central compartment *versus* time (9), the main results of the current approach presented in Eqs. 20a–20e for the time dependence of concentrations of the three compartments are in agreement with the familiar compartment model analysis. However, the significant feature of the hydrodynamic analog is that the physical meaning of the observed slopes, intercepts, and rate coefficients can be presented.

The parameters characteristic of the system are the permeabilities of the barrier between Compartments 1 and 2, δ_{12}, the barrier between Compartments 1 and 3, δ_{13}, the volumes of distribution of drug in the three compartments, V_σ, and the elimination rate constant, k_{20}. One now evidently needs a detailed procedure for evaluating the parameters characteristic of the physiological system and the drug from experimental data. Due to limitations of the experimental procedure in the physiological system, such experimental information is (unfortunately) usually restricted to the time course of the concentration of drug in Compartment 1.

This analysis categorically points out that the usual identification of the asymptotic slope for large times of the plot of ln $X_1(t)$ with the elimination rate constant k_{20} is untenable. This asymptotic slope equals the smallest of the three decay constants, say $(-\mu_3)$ equal to $(k_{20} - r_3)$.

The familiar resolution of the plot of ln X_1 *versus* t, into sum of three linear plots, yields the values of μ_1, μ_2, and μ_3 for the slopes. Corresponding intercepts at time $t = 0$ yield the values of, for example, i_1, i_2, and i_3. These are the known quantities at present from experimental data. Defining the computable quantities j_σ by:

$$\ln j_\sigma = i_\sigma \qquad \text{(Eq. 24a)}$$

$$j_\sigma = C_\sigma(1 + r_\sigma m);\ \sigma = 1, 2, 3 \qquad \text{(Eq. 24b)}$$

one has the values of $C_\sigma(1 + r_\sigma m)$, where m equals (V_2/δ_{12}).

Additional information available from experimental data is the concentration of drug in Compartment 1 at time $t = 0$—*viz.:*

$$X_1(0) = j_1 + j_2 + j_3 = \text{dose}/V_1 \qquad \text{(Eq. 25)}$$

From a knowledge of the initial dose and $X_1(0)$, the volume of distribution of Compartment 1, V_1, is known.

Since μ_1, μ_2, and μ_3 are known, one can compute the quantities A and C:

$$A = k_{20} + \alpha_{12} + \alpha_{13} \qquad \text{(Eq. 26a)}$$

$$C = k_{20}(\delta_{13}/V_3)(\delta_{12}/V_1) \qquad \text{(Eq. 26b)}$$

from the relations:

$$A = -(\mu_1 + \mu_2 + \mu_3) = P + 3k_{20} \qquad \text{(Eq. 27a)}$$

$$C = -(\mu_1\mu_2\mu_3) = k_{20}^3 + k_{20}^2P + k_{20}Q + R \qquad \text{(Eq. 27b)}$$

Equations 26a, 26b, 27a, and 27b follow from recognition of the fact that the decay constants μ_σ's are the three distinct roots of the cubic equation:

$$\mu_\sigma^3 + \mu_\sigma A + \mu_\sigma B + C = 0 \qquad \text{(Eq. 28a)}$$

$$B = \mu_1\mu_2 + \mu_1\mu_3 + \mu_2\mu_3 = Q + 2k_{20}P + 3k_{20}^2 \qquad \text{(Eq. 28b)}$$

[1] Since a critical examination of the physical and mathematical results of the multicompartment hydrodynamic diffusion analog may not be of much interest to the general reader, these aspects are presented in the next paper.

From Eqs. 20*a*–20*e*, 21*a*–21*e*, and 25, one has:

$$X_1(0) = (C_1m)[(\mu_1 - \mu_3) + p(\mu_2 - \mu_3)] \quad \text{(Eq. 29}a\text{)}$$

$$p\{j_1 - (C_1m)(\mu_1 - \mu_2)\} = j_2 \quad \text{(Eq. 29}b\text{)}$$

Elimination of p from Eqs. 29*a* and 29*b* yields a quadratic expression for the unknown (C_1m):

$$(C_1m)^2(\mu_1 - \mu_2)(\mu_1 - \mu_3) - (C_1m)\{j_1(\mu_1 - \mu_3) + j_2(\mu_2 - \mu_3) + X_1(0)(\mu_1 - \mu_2)\} + j_1X_1(0) = 0 \quad \text{(Eq. 30)}$$

Since all quantities except (C_1m) of Eq. 30 are known from experimental information, one can solve for the value of (C_1m). Then p can be solved using:

$$p = (\mu_2 - \mu_3)^{-1}[\{X_1(0)/(C_1m)\} - (\mu_1 - \mu_3)] \quad \text{(Eq. 31)}$$

One has from Eqs. 21*c* and 23*c* two relations relating ω and k_{20}:

$$\omega(\text{dose}/V_1) = (C_1m)\{\mu_1^2 - \mu_3^2) + p(\mu_2^2 - \mu_3^2) + 2k_{20}[(\mu_1 - \mu_3) + p(\mu_2 - \mu_3)]\} \quad \text{(Eq. 32)}$$

$$\omega = 2k_{20} + [\{(\mu_1^2 - \mu_3^2) + p(\mu_2^2 - \mu_3^2)\}/\{(\mu_1 - \mu_3) + p(\mu_2 - \mu_3)\}] \quad \text{(Eq. 33)}$$

Since p and (C_1m) are now known, Eqs. 32 and 33 should be solved simultaneously for ω and k_{20}. From the knowledge of k_{20}, μ_σ, and j_σ, the values of C_σ, r_σ, and m are computed. From the values of V_1 and V_2 thus obtained, δ_{12} can be computed. Since ω is defined in Eq. 21*d*, one can now compute (δ_{13}/V_1). The value of α_{13} is computed using:

$$\alpha_{13} = A - k_{20} - \alpha_{12} \quad \text{(Eq. 34)}$$

The value of (δ_{13}/V_3) is obtained using:

$$(\delta_{13}/V_3) = \alpha_{13} - (\delta_{13}/V_1) = A + \omega - 2k_{20} \quad \text{(Eq. 35)}$$

From these procedures, all parameters characteristic of the three-compartment pharmacokinetic system and drug are thus computed. Since the quadratic Eq. 30 may yield two distinct values of (C_1m), one of these values may be discarded in certain cases as physically meaningless, using the physical realistic condition that the value of α_{13} should be greater than (δ_{13}/V_1).

The physically meaningful condition that α_{13} is greater than (δ_{13}/V_1) leads to the condition that when the two roots of Eq. 30 are distinct, one of them is meaningless. This conclusion is arrived at by the arguments presented in the *Appendix*.

COMPLETE SPECIFICATION OF PARAMETERS IN THREE-COMPARTMENT SYSTEMS

The prescription presented can be systematically characterized as follows. Compute V_1, the volume of distribution of the central compartment, using Eq. 25. Compute the product (C_1m) using Eq. 30, and compute p using Eq. 31. Then compute ω and k_{20} using Eqs. 32 and 33 simultaneously, and compute r_1, r_2, and r_3 using the relations $r_\sigma = \mu_\sigma + k_{20}$.

Compute C_1 using the relation $C_1 = j_1 - r_1(C_1m)$; compute C_2 and C_3 using Eqs. 23*a* and 23*b*, respectively. The sum of $(\alpha_{12} + \alpha_{13})$ and $\{\alpha_{12} + (\delta_{13}/V_1)\}$ are known from Eqs. 34 and 35. Since (δ_{13}/V_3) is also known from Eq. 35, Eq. 26*b* yields the value of (δ_{12}/V_1). Thus, δ_{12} is now known. Since m is known from values of C_1 and (C_1m), V_2 is computable. Thus, calculation of individual values of α_{12} and α_{13} is now feasible with Eq. 26*a*. Compute (δ_{13}/V_1) from knowledge of α_{13} and (δ_{13}/V_3).

CONCLUSIONS

The motivation behind the development of the hydrodynamic diffusion model as an alternative to more familiar pharmacokinetic multicompartment models has been many fold. The present work derived inspiration from the classic work of Northrop and Anson (6).

The similarity of the method of resolution of compound radioactivity into component contributions and familiar multicompartment models of pharmacokinetics is at best only superficial. Radioactive decay processes have the unique advantages that decay constants are independent of environment and that the integration constants encountered are just the concentrations at initial time of independently decaying individual components. In two- or three-compartment models, the integration constants, although proportional to dose, are functions of decay constants.

The decay constants of familiar pharmacokinetics are determined by system parameters such as volumes of distribution of various compartments, permeability properties of barriers partitioning the system into compartments, and the behavior of the drug itself. In familiar compartment models, much of this information is latent in the kinetic rate coefficients, and extraction of physical properties of the system from such rate coefficients is messy. It is also maintained that these decay constants are independent of volumes of distribution in familiar pharmacokinetics. Introduction of five rate constants, while three are sufficient, to describe the flow processes in three-compartment models and balancing gain *versus* loss by forward flow minus backward flow is unnecessary and aesthetically unappealing.

Other motivations behind the present work are to explain possible observations of kinks in the concentration time plot of central compartments (4) and to analyze the theoretical possibility of observation of aperiodic oscillatory phenomena with certain drugs in certain physiological systems. Some of these considerations are presented in the following paper (9). It should be emphasized, however, that observation of even one such kink requires that the drug and the physiological systems simulate a multicompartment system with the number of compartments greater than three.

A reliable method of computation of characteristic parameters of the system from experimental data in preference to the familiar procedure is presented. One can incorporate improvements such as multiple doses given at different times through the central compartment as well as metabolic reactions in various compartments and barriers with which the administered drug can participate. Extension of the method to the multicompartment model is straightforward and naturally tedious. The presented model can be elaborated further to include real situations.

APPENDIX

It is shown here that the physical condition that α_{13} is greater than (δ_{13}/V_1) results always in only one physically meaningful root of Eq. 30. Defining $a = (\mu_1 - \mu_2)$, $b = (\mu_1 - \mu_3)$, $c = (\mu_2 - \mu_3)$, $Y = (C_1m)$, and $d = (\delta_{13}/V_3)$, one has Eqs. 22*a*–22*c* written as:

$$Yab = X_1(0)(d + \mu_1) \quad \text{(Eq. A1}a\text{)}$$

$$Ypac = -X_1(0)(d + \mu_2) \quad \text{(Eq. A1}b\text{)}$$

$$Y(1 + p)bc = -X_1(0)(d + \mu_3) \quad \text{(Eq. A1}c\text{)}$$

The physical condition that α_{13} is greater than (δ_{13}/V_1) demands that d is positive definite. Equations 29*a* and 29*b* become:

$$X_1(0) = Y(b + pc) \quad \text{(Eq. A2}a\text{)}$$

$$p = j_2/(j_1 - Ya) \quad \text{(Eq. A2}b\text{)}$$

Replacing Y in Eqs. A2*a* and A2*b* by the result of Eq. A1*a* yields:

$$j_2c = X_1(0)(d + \mu_1 - a) - j_1b + j_1\{ab/(d + \mu_1)\} \quad \text{(Eq. A3)}$$

The coefficient of (C_1m) of Eq. 30 becomes:

$$X_1(0)(d + \mu_1) + j_1\{ab/(d + \mu_1)\} \quad \text{(Eq. A4)}$$

and the two roots of Eq. 30 are:

$$Y^+ = X_1(0)(d + \mu_1)/ab \quad \text{(Eq. A5}a\text{)}$$

$$Y^- = j_1/(d + \mu_1) \quad \text{(Eq. A5}b\text{)}$$

Thus, solution for (C_1m) expressed by Eq. A5*a* is in agreement with Eq. A1*a*. Since $j_1 = C_1 + C_1m(\mu_1 + k_{20})$, one has from Eq. A5*b* that:

$$1 = m(d - k_{20}) \quad \text{(Eq. A6)}$$

If d is zero or negative, or if d is positive and has a magnitude less than k_{20}, one has the nonphysical result that m should be negative. Thus, the second root of Eq. 30 becomes meaningless

when d is zero or negative. Unless the value of j_1 equals $X_1(0)\{(d + \mu_1)^2/(ab)\}$, the two roots of Eq. 30 will be distinct.

DEFINITION OF SYMBOLS

μ_σ = decay constants of exponentials
r_σ = roots of cubic equation (Eq. 19)
V_σ = volume of distribution of the compartments
C_σ = integration constants proportional to dose
t_1^* = time at which minimum occurs in $X_1(t)$
t_1^{**} = time at which maximum may occur in $X_1(t)$
t_2^* = time at which maximum occurs in $X_2(t)$
t_3^* = time at which maximum occurs in $X_3(t)$; $X_3(t_3^*) = X_1(t_3^*)$
$t(0)$ = time at which extremum occurs in $F(t)$
X_σ = concentration in Compartment σ
i_σ = intercepts of three resolved plots whose sum depicts $\ln X(t)$
δ_{12} = permeability of drug across the barrier between Compartments 1 and 2
$\alpha_{12} = (\delta_{12}/V_1) + (\delta_{12}/V_2)$

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Hydrodynamic Analog Model for Pharmacokinetics II: Critical Examination of Model and Its Contribution to Pharmacokinetics

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Abstract □ A comparison of the conventional pharmacokinetic models and the previously proposed hydrodynamic diffusion analog model is presented. A significant result that an n-compartment system can exhibit at best $(n - 1)$ extremum times in the concentration–time plot of the central compartment under appropriate values of physiological parameters is presented. The observation of kinks experimentally in certain physiological–drug systems is thus shown to be amenable to explanation.

Keyphrases □ Models, hydrodynamic diffusion analog—proposed for pharmacokinetics, critical examination, equations □ Diffusion model, hydrodynamic, analog—proposed for pharmacokinetics, critical examination, equations □ Pharmacokinetics—hydrodynamic diffusion analog model proposed and critically examined, equations

The hydrodynamic analog of the multicompartment model presented previously (1) leads to certain significant conclusions, which agree with the results of the familiar pharmacokinetic models and provide new insights. This article presents a critical examination of this contribution to pharmacokinetics and a possible observation of aperiodic oscillatory phenomena similar to the kink observed in the case of the dicumarol system.

ANALYSIS

Mathematically, both the hydrodynamic analog and familiar multicompartment models essentially involve solutions of coupled first-order linear differential equations of the kind (2):

$$\dot{X}(t) = AX(t) \qquad \text{(Eq. 1)}$$

where X is an n-component vector whose elements represent concentrations at time t of the n-compartment diffusion model (1).

In the familiar pharmacokinetic model, these vector elements represent the amount of substance present in each compartment. The super dot in Eq. 1 denotes the first time derivative. The time-independent elements of matrix A of Eq. 1 represent the permeabilities of the drug in barriers between connected compartments in the hydrodynamic diffusion model. Thus, when there is no connection between Compartments i and j, the corresponding matrix element A_{ij} is zero.

In the familiar pharmacokinetic model, the elements of the corresponding matrix are linear combinations of assumed first-order rate constants. For example, the partial contribution (due to the existence of connectivity with Compartment j) to the rate of decrease in the amount of material in Compartment i is assumed to be given by:

$$\dot{Y}_i = -k_{ij}Y_i + k_{ji}Y_j \qquad \text{(Eq. 2)}$$

where Y_j and Y_i are the amounts in Compartments j and i, respectively, at time t; and the k_{ij}'s are the assumed first-order rate constants.

Thus, volumes of distribution of various compartments are not introduced in the formulation of the familiar pharmacokinetic model and these need to be extracted from experimental data on the basis of *ad hoc* assumptions. The decay constants of conventional pharmacokinetics are considered not as functions of volumes of distribution. Since volumes of distribution of various compartments in an n-compartment model definitely play a role in the material distribution in various compartments at arbitrary finite