Two-Compartment Model for a Drug and Its Metabolite: Application to Acetylsalicylic Acid Pharmacokinetics

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Abstract □ A general solution is presented for solving the pharmacokinetic parameters which describe a drug and its metabolite in a two-compartment open model. The method is specifically applied to the treatment of plasma data for acetylsalicylic acid and its metabolite, salicylic acid, following intravenous administration of acetylsalicylic acid. The acetylsalicylic acid data were found to be adequately described by a model in which elimination occurs solely from the central compartment.

Keyphrases □ Model, two-compartment, open—pharmacokinetic parameters □ Kinetic equations—two-compartment open model □ Acetylsalicylic acid—pharmacokinetics □ Concentration–time curve areas, ratio—drug-metabolite

In a previous publication a comparison of two models was made in an attempt to describe the pharmacokinetics of acetylsalicylic acid (ASA) following an intravenous dose to man (1). An essential feature in both of these models was the distribution of ASA between a central and peripheral compartment while the comparison revolved around deciding whether metabolism to salicylic acid (SA) occurred exclusively in the central compartment (Model A) or in both compartments (Model B, Fig. 1). The third possibility, *i.e.*, metabolism solely in the peripheral compartment, was excluded as hydrolysis is known to occur in plasma, which is the reference system for the central compartment. In addition, it was tacitly assumed that Model A also described SA kinetics for an intravenous dose. Both models were simulated on an analog computer, and from the results it was suggested that only Model A adequately fitted the observed ASA and resultant SA plasma data. Subsequent reexamination of this problem shows that by using both the ASA and SA data, an analytical solution is available for determining all the rate constants for ASA in Model B.

DISCUSSION

Before proceeding with the specific problem, a number of pertinent points can be made relating to the above two simple models, A and B. In either case the same biexponential concentration–time curve results from an intravenous dose of the drug into Compartment 1 and this is characterized by the exponents α' and β' together with the coefficients A′ and B′ as shown in Table I. (The double prime terms used in Model B are numerically equivalent to those in Model A, and serve only to distinguish between the models.) However, whereas these exponents and coefficients allow a complete solution of all the rate constants in Model A, *i.e.*, k_{21}, k_{12}, and k_{13}, only $(k_{21} + k_{24})$, $(k_{12} + k_{13})$, together with the product of k_{12} and k_{21}, can be calculated in Model B. Failure to recognize these boundary conditions in Model B resulted in an incorrect analysis of the analog computer calculations which appeared in Fig. 6 of *Reference 1*. Consequently, by just measuring the unchanged drug, it is impossible to obtain a solution for the specific rate constants in Model B. This may only be achieved by measuring the metabolite derived by biotransformation of the parent drug and by injection of this metabolite on a separate occasion. Such an approach, namely, following a drug and one of its metabolites was used in determining the model necessary to describe the pharmacokinetics of ASA. As expected the intravenous ASA data can be fitted by either Model A or B.

Enlarging this discussion leads to consideration of the more general situation which is represented in Model C (Fig. 2). Here elimination can proceed in both the tissue and peripheral compartments for drug and any metabolite that one measures. Despite this complexity, drug plasma levels still decline biexponentially, but with more rate constants involved in any one term in the equation describing these results (Table II). In this case, as in Model B, if drug alone is measured, it is only possible to calculate the sum of various rate constants, *i.e.*, $(k_{12} + k_{13} + k_{17})$ and $(k_{21} + k_{24} + k_{28})$ together with the product of k_{12} and k_{21}. Likewise, an injection of the metabolite only allows the solution of $(k_{43} + k_{46})$, $(k_{34} + k_{25})$ together with the product of k_{34} and k_{43}. An additional number of rate constants in Model C can, however, be solved by determining the fraction of a dose in Compartment 3 with time following the injection of the parent drug. The general form of this function can be readily derived by solving the differential equations which describe Model C and which are as follows:

$$\dot{F}_1 = -(k_{12} + k_{13} + k_{17})\cdot F_1 + k_{21}\cdot F_2 \quad \text{(Eq. 1)}$$

$$\dot{F}_2 = k_{12}\cdot F_1 - (k_{21} + k_{24} + k_{28})\cdot F_2 \quad \text{(Eq. 2)}$$

$$\dot{F}_3 = k_{13}\cdot F_1 + k_{43}\cdot F_4 - (k_{34} + k_{35})\cdot F_3 \quad \text{(Eq. 3)}$$

$$\dot{F}_4 = k_{24}\cdot F_2 + k_{34}\cdot F_3 - (k_{43} + k_{46})\cdot F_4 \quad \text{(Eq. 4)}$$

$$\dot{F}_5 = k_{35}\cdot F_3 \quad \text{(Eq. 5)}$$

$$\dot{F}_6 = k_{46}\cdot F_4 \quad \text{(Eq. 6)}$$

Table I—Various Parameters Which Define Models A and B in Fig. 1

	Model A	Model B
Plasma (blood) concentration time curve	$C_1 = A'e^{-\alpha' t} + B'e^{-\beta' t}$	$C_1 = A''e^{-\alpha'' t} + B''e^{-\beta'' t}$
Fraction of dose in central compartment	$F_1 = \frac{m_1}{\text{dose}} = \frac{C_1}{A' + B'}$ $= X'_\alpha e^{-\alpha' t} + X'_\beta e^{-\beta' t}$	$F_1 = \frac{m_1}{\text{dose}} = \frac{C_1}{A'' + B''}$ $= X''_\alpha e^{-\alpha'' t} + X''_\beta e^{-\beta'' t}$
Definition of terms with respect to the appropriate model	$X'_\alpha = \frac{k_{21} - \alpha'}{\beta' - \alpha'}$ $\alpha' + \beta' = k_{12} + k_{13} + k_{21}$ $\alpha'\beta' = k_{13}\cdot k_{21}$	$X''_\alpha = \frac{(k_{21} + k_{24}) - \alpha''}{\beta' + \alpha'}$ $\alpha'' + \beta'' = (k_{12} + k_{13}) + (k_{21} + k_{24})$ $\alpha''\beta'' = (k_{12} + k_{13})(k_{21} + k_{24}) - k_{12}\cdot k_{21}$

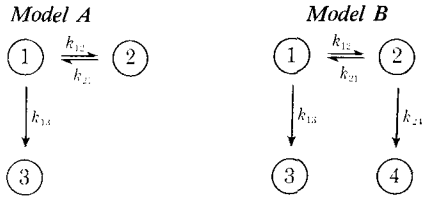

Figure 1—*Two-compartment open system in which elimination of drug, introduced into Compartment 1, occurs either from that compartment (Model A) or from both compartments (Model B).*

$$\dot{F}_7 = k_{17} \cdot F_1 \qquad \text{(Eq. 7)}$$

$$\dot{F}_8 = k_{28} \cdot F_2 \qquad \text{(Eq. 8)}$$

$$\sum_{n=1}^{8} F_n = 1 \qquad \text{(Eq. 9)}$$

$$F = \frac{m_3}{\text{dose}} = X_\alpha e^{-\alpha t} + X_\beta e^{-\beta t} + X_\gamma e^{-\gamma t} + X_\delta e^{-\delta t} \qquad \text{(Eq. 10)}$$

where

$$X_i = \frac{k_{13}(k_{21} + k_{24} + k_{28} - i)(k_{43} + k_{46} - i) + k_{12} \cdot k_{24} \cdot k_{43}}{(j - i)(k - i)(l - i)}$$

and i equals either α, β, γ, or δ, while j, k, and l are the superscripted values not equal to i; *i.e.*, $i = \alpha$:

$$X_\alpha = \frac{k_{13}(k_{21} + k_{24} + k_{28} - \alpha)(k_{43} + k_{46} - \alpha) + k_{12} \cdot k_{24} \cdot k_{43}}{(\beta - \alpha)(\gamma - \alpha)(\delta - \alpha)}$$

Letting $E_2 = k_{21} + k_{24} + k_{28}$; $E_4 = k_{43} + k_{46}$; $A_{13} = k_{12} \cdot k_{24} \cdot k_{43}$, $\therefore$

$$F = k_{13} \sum_{i=\alpha}^{\delta} \frac{(E_2 - i)(E_4 - i)}{(j - i)(k - i)(l - i)} e^{-it} + A_{13} \sum_{i=\alpha}^{\delta} \frac{1}{(j - i)(k - i)(l - i)} e^{-it} \qquad \text{(Eq. 11)}$$

Rearranging

$$\frac{F_3}{\sum_{i=\alpha}^{\delta} \frac{1}{(j - i)(k - i)(l - i)} e^{-it}} = k_{13} \frac{\sum_{i=\alpha}^{\delta} [(E_2 - i)(E_4 - i)]e^{-it}/[(j - i)(k - i)(l - i)]}{\sum_{i=\alpha}^{\delta} e^{-it}/[(j - i)(k - i)(l - i)]} + A_{13} \qquad \text{(Eq. 12)}$$

Since α, β, γ, and δ are known, and the terms $(k_{21} + k_{24} + k_{28})$ and $(k_{43} + k_{46})$ can be determined from the values of the coefficients described in the intravenous data, it is possible to calculate at any given time all the summation terms in Eq. 11, and in the rearranged Eq. 12, an equation for a straight line. Also, since the corresponding values of F_3 may be derived directly from the experimental metabolite plasma data following injection of the parent drug, it is possible to calculate both of the time variable functions on either side of Eq. 12. A plot of these functions will then give a slope of k_{13} and an intercept equal to the product $k_{12}k_{24}k_{43}$. Therefore, even in this relatively complex model, the rate constant k_{13}, describing metabolism within the central compartment to the measured metabolite, can be determined.

Amount of Drug Loss from Compartments 1 and 2—In looking at the general model, it is equally important to know the fraction of the drug which is lost from Compartment 1 and Compartment 2, respectively. These values are simply given as follows:

fraction drug lost from Compartment 1 =

$$(k_{13} + k_{17}) \int_0^\infty F_1 \, dt \qquad \text{(Eq. 13)}$$

Table II—Various Parameters Which are Characteristic of Model C in Fig. 2

Concentration–time curve of drug in Compartment 1.	$C_1 = Ae^{-\alpha t} + Be^{-\beta t}$
Fraction of dose in Compartment 1.	$F_1 = X_\alpha e^{-\alpha t} + X_\beta e^{-\beta t}$
Definition of coefficient and exponents for drug introduced as a bolus *via* Compartment 1.	$X_\alpha = \frac{(k_{21} + k_{24} + k_{28}) - \alpha}{\beta - \alpha}$ $\alpha\beta = (k_{12} + k_{13} + k_{17}) \times (k_{21} + k_{24} + k_{28}) - k_{12} \cdot k_{21}$
Concentration–time curve of metabolite introduced as a bolus *via* Compartment 3.	$C_3 = Ce^{-\gamma t} + De^{-\delta t}$
Corresponding fraction of metabolite in Compartment 3.	$F_3 = X_\gamma e^{-\gamma t} + X_\delta e^{-\delta t}$
Corresponding definition of coefficient and exponents for metabolite.	$X_\gamma = \frac{(k_{43} + k_{46}) - \gamma}{\delta - \gamma}$ $\gamma + \delta = (k_{43} + k_{46}) + (k_{34} + k_{35})$ $\gamma\delta = (k_{43} + k_{46})(k_{34} + k_{35}) - k_{34} \cdot k_{43}$

fraction drug lost from Compartment 2 =

$$(k_{24} + k_{28}) \int_0^\infty F_2 \, dt \qquad \text{(Eq. 14)}$$

Since the values of F_1 and F_2 are given by:

$$F_1 = \frac{E_2 - \alpha}{\beta - \alpha} e^{-\alpha t} + \frac{E_2 - \beta}{\alpha - \beta} e^{-\beta t} \qquad \text{(Eq. 15)}$$

$$F_2 = \frac{k_{12}}{\beta - \alpha} e^{-\alpha t} + \frac{k_{12}}{\alpha - \beta} e^{-\beta t} \qquad \text{(Eq. 16)}$$

it follows that:

$$\text{fraction drug lost from Compartment 1} = \frac{(k_{13} + k_{17})E_2}{\alpha\beta} \qquad \text{(Eq. 17)}$$

$$\text{fraction drug lost from Compartment 2} = \frac{k_{12}(k_{24} + k_{28})}{\alpha\beta} \qquad \text{(Eq. 18)}$$

Also, as expected, addition of Eqs. 17 and 18 and appropriate substitution shows that the sum of the fractions of drug lost from Compartments 1 and 2 is unity.

Clearance of Drug from Compartments 1 and 2—The total body clearance (TBC) of drug, defined by Eq. 19, is model independent for an i.v. dose no matter where drug loss occurs.

$$\text{TBC} = \frac{\text{dose}}{\int_0^\infty C_1 \, dt} \qquad \text{(Eq. 19)}$$

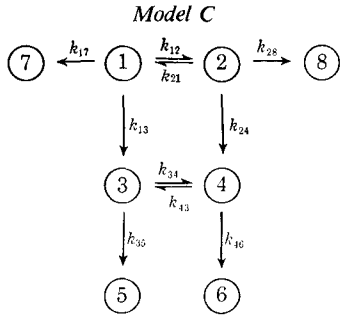

Figure 2—*Compartmental model describing the distribution and elimination of a drug injected into Compartment 1, elimination proceeding by various routes from Compartments 1 and 2, with a metabolite, 3, undergoing analogous disposition.*

Table III—Ratio of the Total Areas under the Metabolite Concentration–Time Curve following an Equimolar i.v. Dose of Drug and Metabolite

Case	Model: $k_{46}>0$	Model: $k_{46}=0$	Ratio of Areas[a]: $k_{46}>0$	Ratio of Areas[a]: $k_{46}=0$
General	I	VI	I $\frac{k_{13}(k_{21}+k_{24}+k_{28})(k_{43}+k_{46})+k_{12}k_{24}k_{43}}{\alpha\beta(k_{43}+k_{46})}$	VI $\frac{k_{13}(k_{21}+k_{24}+k_{28})+k_{12}k_{24}}{\alpha\beta}$
$k_{28}=0$	II	VII	II $\frac{k_{13}(k_{21}+k_{24})(k_{43}+k_{46})+k_{12}k_{24}k_{43}}{\alpha\beta(k_{43}+k_{46})}$	VII $\frac{k_{13}(k_{21}+k_{24})+k_{12}k_{24}}{\alpha\beta}$
$k_{17}=k_{28}=0$	III	VIII	III $\frac{k_{13}(k_{21}+k_{24})(k_{43}+k_{46})+k_{12}k_{24}k_{43}}{\alpha\beta(k_{43}+k_{46})}$	VIII 1
$k_{24}=k_{28}=0$	IV	IX	IV $\frac{k_{13}}{k_{13}+k_{17}}$	IX $\frac{k_{13}}{k_{13}+k_{17}}$
$k_{17}=k_{24}=k_{28}=0$	V	X	V 1	X 1

[a] In the formulas, $\alpha\beta = E_1E_2 - k_{12}\cdot k_{21}$

Multiplying both sides of Eq. 13 by dose divided by V_1, the volume constant for Compartment 1 [*i.e.*, V_1 = dose/$(A + B)$], gives:

$$\frac{\text{(amount of drug lost from Compartment 1)}}{V_1} = (k_{13} + k_{17})\int_0^\infty C_1 dt \qquad \text{(Eq. 20)}$$

Rearranging Eq. 20 results in:

clearance of drug from Compartment 1 = $(k_{13} + k_{17})\,V_1$ (Eq. 21)

Subtracting Eq. 21 from Eq. 19 yields the clearance of drug from Compartment 2, which may also be numerically given by:

clearance of drug from Compartment 2 = $(k_{24} + k_{28})\,V_2$ (Eq. 22)

where V_2, the volume constant for distribution in Compartment 2 with reference to the concentration in Compartment 1, is defined as

$$V_2 = \frac{k_{12}}{E_2}V_1 \qquad \text{(Eq. 23)}$$

Although the volume terms V_1 and V_2 may not be equal to a real physiological space, the clearances from Compartments 1 and 2 (as defined in Eqs. 21 and 22) are measures of an actual clearance for organs and/or tissues within the body.

Area Analysis—Assuming that the rate constants defining the kinetics of the metabolite are independent of whether it is given directly or formed by the biotransformation of the parent compound, one can calculate the ratio of the total areas under the metabolite concentration–time curve in Compartment 3 following an equivalent dose of parent drug and metabolite on separate occasions. This is given by

$$\text{ratio of metabolite areas} = \frac{\left[\int_0^\infty F_3\,dt\right]_{\text{i.v. drug}}}{\left[\int_0^\infty F_3\,dt\right]_{\text{i.v. metabolite}}} = \frac{k_{13}E_2E_4 + A_{13}}{\alpha\beta E_4} \qquad \text{(Eq. 24)}$$

Utilizing such an equation, it is possible to investigate the influence of the route and magnitude of elimination and distribution on the area under the metabolite curve. Several such cases are illustrated in Table III. Cases IX and X represent the well-known models in which elimination of the drug (and metabolite) occurs solely from

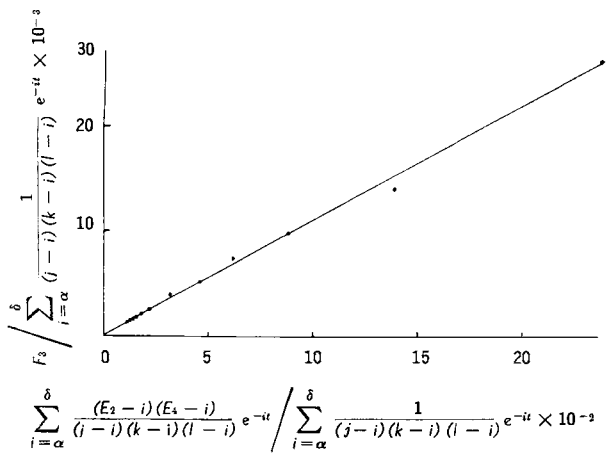

Figure 3—*Plot of the time variable functions in Eq. 13, Subject A. Slope equal to* k_{13}.

Table IV—Values Calculated to Test the Model Appropriate for ASA Pharmacokinetics

Subject	k_{13} (min.$^{-1}$) Model A[a]	k_{13} (min.$^{-1}$) Model C[b]	$k_{12}k_{24}k_{43}$[b]	k_{24}[c]	Fraction ASA Metabolized in Compartment 1[d]	Fraction ASA Metabolized in Compartment 2[e]
A	0.117	0.113	1×10^{-4}	0.005	0.95	0.05
B	0.101[f]	0.095	3×10^{-4}	0.009	0.94	0.06
C	0.096[f]	0.110	-4×10^{-4}	−0.025	1.14	−0.14
D	0.105	0.095	2×10^{-4}	0.014	0.91	0.09

[a] Taken from Reference 1. [b] Calculated by graphical methods utilizing Eq. 12. [c] Calculated using equations defined for Model B in Table I and graphical solution for k_{13}. [d] Calculated using Eq. 17 when $k_{17} = 0$. [e] Calculated using Eq. 18 when $k_{28} = 0$. [f] These values differ slightly from those reported previously (1) due to calculation errors.

the central compartment. Case IX is normally used to calculate the rate constant, k_{13}, when the sum $(k_{13} + k_{17})$ has been determined from previous i.v. data. When the ratio of areas is unity, it is impossible to distinguish between Cases V, VIII, and X. The remaining cases illustrate those conditions in which elimination of an unchanged drug also occurs from Compartment 2 and metabolite may or may not be eliminated from Compartment 4. Table III clearly shows that the corresponding area analysis cannot be used to calculate exclusively the rate constant k_{13}. Rather this ratio of areas under the metabolite concentration–time curve is a complex function which results from the interplay of all the constants in the appropriate model.

Examination of ASA Kinetics—Returning to the problem associated with the ASA data, the total area under the SA plasma concentration–time curve was the same following either injection of ASA or an equivalent dose of SA. Also, it has been reported that only approximately 1% of ASA is eliminated unchanged in the urine (2). These data, in themselves, suggest that all the models in Table III can be excluded with the exception of Cases V, VIII, and X. To distinguish Case VIII from the other two, it is necessary to determine whether the rate constant k_{24} exists. This was ascertained for each of the four subjects in the study (1) by graphically solving Eq. 12. The values for the fraction of the dose in Compartment 3 were obtained by dividing the plasma concentration values for SA by the sum of the coefficients C and D, *i.e.*, $F_3 = C_3/C + D$, while each of the time variable summation terms was calculated at each time point. Figure 3 illustrates such a plot for Subject A of *Reference 1*. As expected, a straight line was obtained for this and the other subjects and resultant values for k_{13} are shown in Table IV together with the intercept $k_{12}k_{43}k_{24}$. In addition, the values for k_{13}, assuming Model A for ASA, are presented. As can be seen the intercept was essentially zero for all subjects, indicating that the term k_{24} is small since the other rate constants, k_{43} and k_{12}, must be positive and significant values as they are related to the distribution of ASA and SA where both of these drugs exhibit biexponential curves. Knowing k_{13}, it is also possible to obtain an exact solution of k_{24} for the ASA data by appropriate substitution into the defined terms for Model B in Table I. These values are presented in Table IV.

From the data in Table IV, it is obvious that the pathway designated by k_{24} may be considered of only minor importance in ASA pharmacokinetics. It is likely that the values reported for k_{24} and the "Fraction ASA Metabolized in Compartment 2" differ from zero only as a result of the errors inherent in the biological experiment. This is reinforced by the negative values calculated for Subject C. Consequently, we are led to the conclusion that Model A rather than Model B describes the ASA data, and this is confirmed by the close similarity between the values of the rate constant, k_{13}, determined by the graphical solution of Eq. 12 and those given by simple calculation based on Model A. Accordingly, as previously suggested (1) the ASA i.v. data can be adequately described by the model in which elimination occurs solely in the central compartment. However, because the rate constant k_{24} appears to be zero, one cannot distinguish between Cases V and X where SA is eliminated exclusively from the central compartment or from both compartments. Obviously were the value of k_{24} a significant number, then k_{43} and hence k_{46} could have been calculated allowing the entire ASA model to be characterized.

TERMINOLOGY

n	refers to Compartment n.
C_n, M_n, F_n	are the corresponding concentration, mass, and fraction of administered dose of a species in compartment n.
k_{nm}	first-order rate constant for the transfer of species from Compartment n to m.
α, β, A, B	are the exponents and coefficients of the equation describing the changes with time for the species in Compartment 1 following an injection of drug into that compartment.
γ, δ, C, D	are the exponents and coefficients of the equation describing the changes with time for the species in Compartment 3 following an injection of metabolite into that compartment.
$\alpha, \alpha', \alpha'', etc.$	are numerically equivalent and the prime terms are solely used to distinguish between various models describing the observed data.
E_n	is the sum of all the rate constants out of compartment n.
A_{nm}	is the product of the rate constants involved in the alternate route between compartments n and m, *i.e.*, $A_{13} = k_{12} \cdot k_{24} \cdot k_{43}$.

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