Pharmacokinetic Basis for the Influence of Route of Administration on the Area Under the Plasma Concentration-Time Curve

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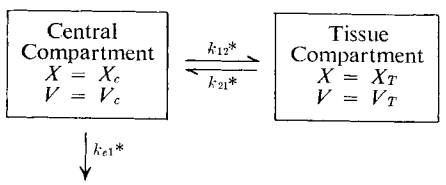
Abstract □ A three-compartment open system is proposed to explain the influence of route of administration (*i.e.*, intravenous *versus* oral) on the area under the plasma concentration-time curve. The hepatoportal system is treated as a compartment distinct from the vascular site being sampled. Computer analysis of the model using estimated pharmacokinetic parameters provided a successful prediction of the relative area under the plasma concentration-time curves after oral and intravenous administration of aspirin in man. It is shown also that the proposed model yields a plasma concentration-time curve after intravenous administration which may be described adequately by a biexponential equation under experimental conditions.

Keyphrases □ Plasma concentration-time curve area—administration route influence □ Pharmacokinetics—administration route effect on plasma concentration-time curve area □ Aspirin plasma concentration *versus* time, simulation—computer analysis □ Model, three-compartment—administration route influence, plasma concentration-time curve area

The two-compartment open model (Model I, Fig. 1), first related to drug pharmacokinetics by Teorell (1), adequately describes the plasma concentration-time data observed after intravenous administration of a large number of drugs. Accordingly, as noted by Riegelman *et al.* (2), Model I probably represents the simplest model for a reasonably sophisticated description of the time course of many drugs in the body, although the still simpler one-compartment model provides certain pharmacokinetic parameters which are indeed useful, particularly in clinical applications.

Occasions may arise however where additional data are available which cannot be reconciled with the two-compartment open model despite the fact that the plasma concentration-time curve is well-described by a biexponential equation and there is little if any statistical justification in using a higher order equation to describe the plasma data. One possible example has been presented by Levy *et al.* (3), who demonstrated how a combination of pharmacologic effect data and drug concentrations in the plasma, as a function of time, could reveal the existence of a three-compartment system which is simply not detected by an analysis of the plasma concentration data alone. As discussed by these authors, it is virtually impossible, in most instances to distinguish between a two-compartment system and more complex pharmacokinetic systems on the basis of plasma concentrations alone.

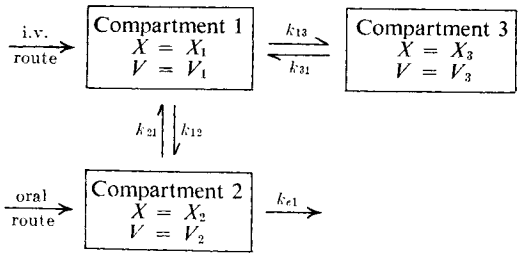


Model I

Figure 1—*Two-compartment open model.* X *is the amount of drug in a given compartment,* V *is the volume of the compartment,* k_{12}^* *and* k_{21}^* *are first-order transfer rate constants and* k_{e1}^* *is the first-order elimination rate constant. Elimination is assumed to occur in the central compartment. For the instantaneous intravenous administration case, at* $t = 0$, $X_T = 0$ *and* $X_c = X^0 =$ *dose.*

A problem similar to that described above occurs when one attempts to rationalize the influence of route of administration on the area under the plasma concentration-time curves of certain drugs, with the two-compartment model which describes the time course of the drug in the plasma after intravenous administration (4, 5). The physiologic basis of the two-compartment model is that the central compartment (see Fig. 1) consists of the plasma as well as a highly perfused lean tissue group which includes the kidney and hepatoportal system. Hence, from a mathematical viewpoint it can be assumed that the parameters of distribution and elimination remain constant after administering the same quantity of drug to the body by different routes, *e.g.*, intravenous and oral. If the areas under the plasma concentration-time curves are not equal, one must conclude that at least one of the following situations exist: (*a*) one or more of the distribution or elimination processes cannot be described by first-order kinetics; (*b*) there is incomplete absorption of the intact drug from the oral route of administration; (*c*) the two-compartment open system (Fig. 1) is inadequate to describe the pharmacokinetics of distribution and elimination of the drug.

The present report deals with the latter situation and provides a mathematical basis for quantifying the influence of route of administration on the area under the plasma level-time curve. Harris *et al.* (5) found that the area under the plasma concentration-time curve of aspirin in dogs upon administration of the drug into the hepatic portal vein was 54–78% that observed after administration of equivalent doses *via* the vena cava. Administration of a drug directly into the hepatic portal vein is, in most instances, equivalent to the pathway followed after oral administration if one assumes complete absorption and an absence of drug metabolism in the intestinal wall. These authors conclude that more of the intact compound reaches the vascular site being sampled by one route than by the other and that the hepatic portal vein route results in the drug passing through an organ, *i.e.*, the liver, which will metabolize part of the compound before it reaches the sampling site. These findings represent a significant contribution to pharmacokinetics and strongly suggest that a model more complex than that shown in Fig. 1 is required to describe the time course of drugs which are rapidly and/or extensively metabolized in the body.



Model II

Figure 2—*Three-compartment open model. The physiologic significance of each compartment is discussed in the text. Pharmacokinetic parameters are defined in Fig. 1. Elimination is assumed to occur in the hepatoportal system (Compartment 2).*

THEORETICAL

If one assumes that the lack of corresponding areas under the plasma concentration-time curves, as a function of route of administration, is principally due to a "first pass effect," as suggested by Harris *et al.* (5), then the model (Model II) shown in Fig. 2 should provide a first approximation of the situation. Compartment 1 may represent the central plasma pool as defined by Price *et al.* (6), the plasma, or the plasma and certain visceral organs not including the liver. Compartment 2 represents the hepatoportal system and in certain instances (where a drug is eliminated essentially exclusively by the hepatoportal system) may also represent the viscera. Compartment 3 represents the "tissue," *i.e.*, a group of tissues which are less rapidly accessible to the drug than the visceral organs. Price (6) suggests that the "tissue" compartment consists of muscle and fat tissues which are rather poorly perfused.

Area Under the Plasma Concentration-Time Curve After Intravenous (e.g., Vena Cava) Administration—In this case the amount of drug in Compartment 1 at time zero is equal to the dose, X^0, while the zero time levels of drug in the other compartments are zero. According to Nagashima *et al.* (7) the plasma concentration (*i.e.*, the concentration of drug in Compartment 1) is given by

$$C_p = C_p^0 [C_1 \exp(-\pi t) + C_2 \exp(-\alpha t) + C_3 \exp(-\beta t)] \quad \text{(Eq. 1)}$$

where C_p is the plasma concentration at any time t, C_p^0 is the plasma concentration at time zero and the other constants are as defined in the appendix.

The total area under the plasma concentration-time curve is defined in terms of the three-compartment model, shown in Fig. 2, in the following manner.

$$(\text{area})_{\text{i.v.}} = \int_0^\infty C_p dt = C_p^0 \left[\int_0^\infty C_1 \exp(-\pi t) + C_2 \exp(-\alpha t) + C_3 \exp(-\beta t) \right] \quad \text{(Eq. 2)}$$

Integration of Eq. 2 yields

$$(\text{area})_{\text{i.v.}} = C_p^0 \left(\frac{C_1}{\pi} + \frac{C_2}{\alpha} + \frac{C_3}{\beta} \right) \quad \text{(Eq. 3)}$$

Substituting for C_1, C_2, C_3 and π, α, and β in terms of the rate constants for Model II (see *Appendix* for appropriate relationships) yields

$$(\text{area})_{\text{i.v.}} = C_p^0 (k_{21} + k_{e1})/k_{12}k_{e1} \quad \text{(Eq. 4)}$$

Since C_p^0 is given by the quotient of the dose and the volume of Compartment 1 (V_1), then

$$(\text{area})_{\text{i.v.}} = \text{dose}\ (k_{21} + k_{e1})/V_1 k_{12} k_{e1} \quad \text{(Eq. 5)}$$

Area Under the Plasma Concentration-Time Curve After Hepatic Portal Vein or Oral Administration—To simplify the kinetic treatment it will be assumed that both routes may be treated in exactly the same fashion, *i.e.*, oral administration results in complete and instantaneous absorption, exclusively *via* the hepatoportal system. Then, from a mathematical point of view, the initial conditions for Model II in this case are as follows: at $t = 0$, $X_1 = X_3 = 0$, and $X_2 = X^0 = \text{Dose}$.

As shown in the *Appendix* (see Eq. 16*a*) the plasma concentration at any time is given by

$$C_p = \frac{\text{dose}}{V_1} \times [C_1' \exp(-\pi t) + C_2' \exp(-\alpha t) + C_3' \exp(-\beta t)] \quad \text{(Eq. 6)}$$

since at any time $C_p \cdot V_1 = X_1$.

The total area under the plasma concentration-time curve upon oral or hepatic vein administration is given by

$$(\text{area})_{\text{oral}} = \frac{\text{dose}}{V_1} \left(\frac{C_1'}{\pi} + \frac{C_2'}{\alpha} + \frac{C_3'}{\beta} \right) \quad \text{(Eq. 7)}$$

Substituting for C_1', C_2', and C_3' and π, α, and β in terms of the rate constants for Model II (see *Appendix* for appropriate relationships) yields

$$(\text{area})_{\text{oral}} = \text{dose}\ (k_{21})/V_1 k_{12} k_{e1} \quad \text{(Eq. 8)}$$

Comparison of Areas Under the Plasma Concentration-Time Curves After Intravenous and Oral Administration—Dividing Eq. 8 by Eq. 5 yields the following relationship

$$(\text{area})_{\text{oral}}/(\text{area})_{\text{i.v.}} = k_{21}/(k_{21} + k_{e1}) \quad \text{(Eq. 9)}$$

where the rate constants are as defined in Model II. Equation 9 clearly shows that the ratio of areas will always be less than unity. The magnitude of this difference is dependent on the ratio of k_{21}/k_{e1}. If this ratio is greater than ten then the simpler model shown in Fig. 1 will adequately describe the overall pharmacokinetics of the drug. If this is not the case, a more complex model is required in which the hepatoportal system is defined as a compartment or part of a compartment which is kinetically distinct from the vascular site being sampled.

COMPUTER ANALYSIS OF ASPIRIN DATA ACCORDING TO MODEL II

Simulated plasma concentration data as a function of time after oral and intravenous administration of aspirin were obtained by using the appropriate differential equations (viz., Eqs. 10*a*, 11*a*, and 12*a*) as input data for the "MIMED" digital computer analog simulation program (8). The rate constants of Model II were estimated from literature data (9), as discussed in the *Appendix*. The rate constants used in the simulation are as follows:

$$k_{12} = 0.700\ \text{min.}^{-1}$$
$$k_{21} = 0.618\ \text{min.}^{-1}$$
$$k_{13} = 0.180\ \text{min.}^{-1}$$
$$k_{31} = 0.123\ \text{min.}^{-1}$$
$$k_{e1} = 0.209\ \text{min.}^{-1}$$

Compartment 1 was assumed to represent the plasma and assigned a volume of 3 l. To obtain a satisfactory graphical relationship of the plasma data as a function of route of administration, the drug was introduced into either Compartment 1 or 2 in a first-order fashion with a rate constant of 0.07 min.$^{-1}$, chosen arbitrarily. The "MIMED" program also provided an estimate of the areas under the simulated plasma concentration *versus* time curve from $t = 0$ to $t = 500$ min. (essentially $t = 0$ to $t = \infty$) by means of a fourth-order Runge-Kutta numerical integration algorithm (8).

The simulated plasma concentrations after administration of 100 mg. aspirin into Compartment 1 (the plasma, intravenous route) and into Compartment 2 (the viscera, oral route) are shown in Fig. 3. The difference between the areas under the plasma concentration-time curves as a function of route of administration is clear. Also quite apparent is that this difference in area does *not* represent a poorer "availability" of aspirin to the body when administered *via* the oral route.

The computer program provided the following area data; $(\text{area})_{\text{oral}} = 140.8$ mg.-min./l. and $(\text{area})_{\text{i.v.}} = 188.4$ mg.-min./l. The area obtained from oral administration is 74.7% that obtained from intravenous administration. This estimate is in perfect agree-

ment with the value of $(\text{area})_{oral}/(\text{area})_{i.v.}$ calculated by means of Eq. 9.

Comparison of the relative areas of the plasma concentration-time curves after oral and intravenous administration based on Model II with absorption data in the literature was most encouraging. Rowland *et al.* (4) report that the areas under the aspirin plasma concentration-time curves in four human subjects after oral administration of 650 mg. of the drug were 65–74% those obtained after an intravenous dose. That aspirin was completely absorbed from the oral dose was demonstrated by the equal areas under the plasma concentration-time curves obtained from the metabolite salicylic acid after the two modes of administration of aspirin. These findings are in excellent agreement with the area ratio of 75% calculated using Model II. Agreement is even better when one considers that the estimate of 75% represents a maximum value based on the assumption that transfer of drug from the plasma to the viscera is blood flow rate limited.

Distinction Between Two-Compartment (Model I) and Three-Compartment (Model II) Models Based on Plasma Level Data—Levy *et al.* (3) have stated that it is frequently impossible to distinguish between a two-compartment and more complex pharmacokinetic system on the basis of plasma concentrations alone. To test this possibility the following calculations were performed. Simulated plasma concentrations at 5-min. intervals after instantaneous intravenous injection of 100 mg. aspirin were obtained with the "MIMED" program using Model II as a basis (initial conditions $X_1 = 100$ mg., $X_2 = X_3 = 0$). These data were intended to simulate "typical" plasma data obtained after intravenous administration of a drug. In such cases a biexponential curve is the usual result. These simulated plasma concentrations were given equal weight and were used as input data for the digital computer program of Marquardt (10) to provide a biexponential least squares regression fit to the data. This yielded the following expression:

$$C_p = 9.60 \exp(-0.264t) + 6.27 \exp(-0.045\ t) \quad \text{(Eq. 10)}$$

with a zero-time intercept of 15.87 mg./l. The apparent excellence of this fit is reflected in the extremely small value of the sum of the squared deviations of the simulated from the calculated plasma concentrations—*viz.*, 2.2×10^{-4}.

Figure 4 depicts the plasma concentrations of aspirin predicted by the biexponential equation and the "MIMED" simulation of Model II. A distinction between the two curves can only be made on the basis of experimental data obtained during the first 2 or 3 min. after injection providing that blood mixing problems (11) do not interfere. Hence from an experimental point of view it is entirely reasonable to obtain an apparently biexponential curve after intravenous administration yet be dealing with a three-compartment model such as Model II.

A final verification of the model and the simulation procedures is obtained by comparing the biexponential equation obtained with the simulated plasma data taken at 5-min. intervals after administration, with literature data (9). After intravenous administration of 650 mg. of aspirin in man the plasma concentration-time curve may be described by the following equation (9):

$$C_p = 58.0 \exp(-0.267\ t) + 28.5 \exp(-0.049t) \quad \text{(Eq. 11)}$$

with a zero time intercept of 86.5 mg./l. Considering that both Eqs. 10 and 11 are of the form $C_p = A \exp(-\alpha t) + B \exp(-\beta t)$, it may be noted that there is excellent agreement of both α and β terms between the two equations. Correcting Eq. 11 to a dose level equivalent to that used to obtain Eq. 10 yields $A = 8.92$ and $B = 4.34$. Both of these values are somewhat lower than, but in reasonable agreement with corresponding values in Eq. 10.

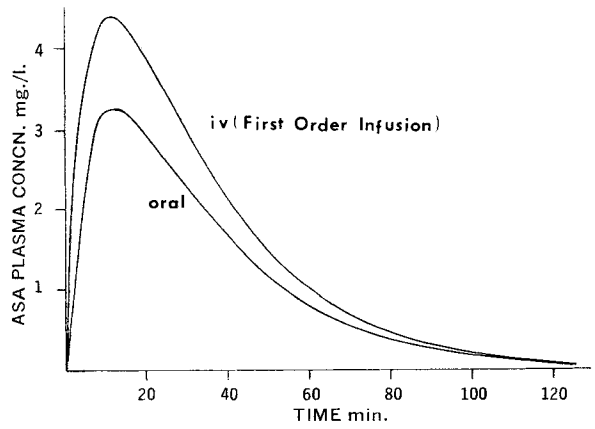


Figure 3—*Simulated plasma concentrations of aspirin (ASA) upon administration of a 100-mg. dose into Compartment 1 (i.v., upper curve) or Compartment 2 (oral, lower curve). In each case the drug is administered in a first-order fashion with a rate constant of 0.07 min.*$^{-1}$.

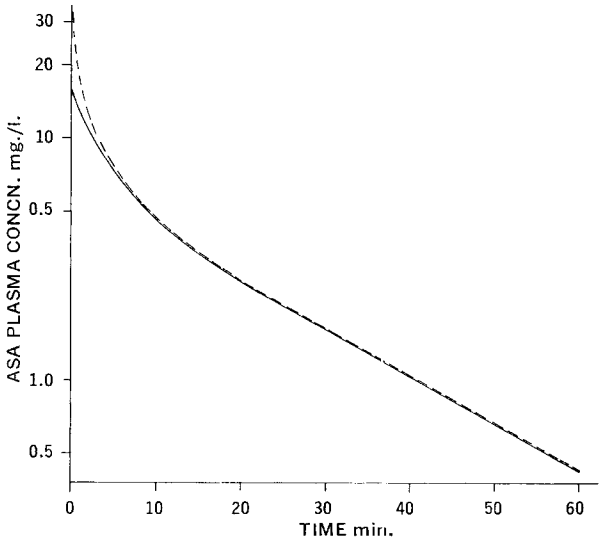


Figure 4—*Semilogarithmic plot of plasma concentrations of aspirin (ASA) versus time calculated according to the "MIMED" simulation of Model II (interrupted line) and the biexponential least squares fit of simulated plasma concentration data taken at 5-min. intervals after instantaneous intravenous injection of 100 mg. aspirin (solid line). See text for further discussion.*

CONCLUSIONS

The three-compartment model, shown in Fig. 2, in which the hepatoportal system is defined as a compartment or part of a compartment which is distinct from the compartment containing the plasma, provides a pharmacokinetic basis to explain the influence of route of administration on the area under the plasma concentration-time curve. The findings support the position taken by Harris *et al.* (5) that one must use caution in applying the law of corresponding areas as developed by Dost (12) and Gladtke (13, 14) to the assessment of drug absorption from the gastrointestinal tract.

APPENDIX

Definition of Constants in Equation 1—According to Nagashima *et al.* (7)

$$C_1 = (K_2 - \pi)(K_3 - \pi)/(\beta - \pi)(\alpha - \pi) \quad \text{(Eq. 1}a\text{)}$$

$$C_2 = (K_2 - \alpha)(K_3 - \alpha)/(\pi - \alpha)(\beta - \alpha) \quad \text{(Eq. 2}a\text{)}$$

$$C_3 = (K_2 - \beta)(K_3 - \beta)/(\alpha - \beta)(\pi - \beta) \quad \text{(Eq. 3}a\text{)}$$

where

$$K_1 = k_{12} + k_{13} \quad \text{(Eq. 4}a\text{)}$$

$$K_2 = k_{e1} + k_{21} \quad \text{(Eq. 5}a\text{)}$$

$$K_3 = k_{31} \quad \text{(Eq. 6}a\text{)}$$

and

$$\pi + \alpha + \beta = K_1 + K_2 + K_3 \quad \text{(Eq. 7}a\text{)}$$

$$\pi\beta + \alpha\beta + \pi\alpha = K_1K_2 + K_1K_3 + K_2K_3 - k_{12}k_{21} - k_{13}k_{31} \quad \text{(Eq. 8}a\text{)}$$

$$\pi\alpha\beta = K_1K_2K_3 - k_{13}k_{31}K_2 - k_{12}k_{21}K_3 \quad \text{(Eq. 9a)}$$

Determination of Drug Levels in Compartment 1 of Model II After Oral Administration—The transfer and elimination processes in the three-compartment open model shown in Fig. 2 may be described as follows:

$$\frac{dX_1}{dt} = -K_1X_1 + k_{21}X_2 + K_3X_3 \quad \text{(Eq. 10a)}$$

$$\frac{dX_2}{dt} = k_{12}X_1 - K_2X_2 \quad \text{(Eq. 11a)}$$

$$\frac{dX_3}{dt} = k_{13}X_1 - K_3X_3 \quad \text{(Eq. 12a)}$$

where K_1, K_2, and K_3 are defined in Eqs. 4*a*, 5*a*, and 6*a*.

Assuming that the dose is administered directly into the hepatoportal system (*i.e.*, Compartment 2) then the Laplace transforms of Eqs. 10*a*, 11*a*, and 12*a* are given by

$$s\bar{X}_1 - 0 = -K_1\bar{X}_1 + k_{21}\bar{X}_2 + K_3\bar{X}_3 \quad \text{(Eq. 13a)}$$

$$s\bar{X}_2 - X^0 = k_{12}\bar{X}_1 - K_2\bar{X}_2 \quad \text{(Eq. 14a)}$$

$$s\bar{X}_3 - 0 = k_{13}\bar{X}_1 - K_3\bar{X}_3 \quad \text{(Eq. 15a)}$$

The above simultaneous transformed differential equations may be solved using the methods of determinants (see *Reference* 7 for a more detailed discussion) to yield X_1, X_2, and X_3. The fraction of the dose in the central compartment at time t is given by

$$\frac{X_1}{X^0} = C_1' \exp(-\pi t) + C_2' \exp(-\alpha t) + C_3' \exp(-\beta t) \quad \text{(Eq. 16a)}$$

where

$$C_1' = k_{21}(K_3 - \pi)/(\beta - \pi)(\alpha - \pi) \quad \text{(Eq. 17a)}$$

$$C_2' = k_{21}(K_3 - \alpha)/(\pi - \alpha)(\beta - \alpha) \quad \text{(Eq. 18a)}$$

$$C_3' = k_{21}(K_3 - \beta)/(\alpha - \beta)(\pi - \beta) \quad \text{(Eq. 19a)}$$

and π, α, and β are related to the intrinsic rate constants as shown in Eqs. 7*a*, 8*a*, and 9*a*.

Estimations of the Rate Constants of Model II for Aspirin—Riegelman *et al.* (9) have found that the two-compartment open model shown in Fig. 1 satisfactorily describes the time course of aspirin in the plasma after intravenous administration. These workers calculated the following pharmacokinetic parameters; $k_{12}^* = 0.085$ min.$^{-1}$, $k_{21}^* = 0.123$ min.$^{-1}$, $k_{el}^* = 0.111$ min.$^{-1}$, and $V_c = 6.4$ l., where V_c is the volume of the central compartment. The volume of the tissue compartment (V_T) of the two-compartment open model, calculated according to Wagner (15, 16), is 4.4 l.

Assuming that the total volume of Compartments 1 and 2 in Model II is comparable to the volume of the central compartment in Model I, and that Compartment 1 corresponds to the plasma, then $V_1 = 3.0$ l. and $V_2 = 3.4$ l. Further assuming that Compartment 3 in Model II is identical to the tissue compartment in Model I, and that clearance from each of these compartments is identical, then $V_3 = V_T = 4.4$ l. and $k_{21}^* = k_{31} = 0.123$ min.$^{-1}$. The elimination rate constant, k_{el}, in Model II was estimated by setting $k_{el} \cdot V_2$ equal to the previously reported (9) value of 0.71 l./min. for the body clearance of aspirin. In this manner it was estimated that $k_{el} = 0.209$ min.$^{-1}$.

The rate constant for transfer of drug from Compartment 1 to Compartment 3, k_{13}, was determined by assuming that clearance from one compartment to another is equal in both directions (15, 16), *i.e.*, $k_{13}V_1 = k_{31}V_3$. Accordingly, $k_{13} = 0.180$ min.$^{-1}$.

An estimate of k_{12} was made by assuming that the transfer of drug from Compartment 1 to Compartment 2 was blood flow limited. According to Price (6), blood flow rate to the viscera (which is essentially equivalent to Compartment 2 in Model II for the aspirin case) is 3.75 l./min./1.73 $m.^2$ in man. Considering a hematocrit value of 45% (17), the visceral plasma flow rate is 2.1 l./min. It is therefore highly probable (18) that $k_{12}V_1 \leqslant 2.1$ l./min. and $k_{12} \leqslant 0.700$ min.$^{-1}$. In the absence of knowledge to the contrary, the transfer was assumed to be blood flow rate limited and k_{12} set equal to 0.700 min.$^{-1}$ Finally, k_{21} was estimated to be 0.618 min.$^{-1}$ by assuming that $k_{12}V_1 = k_{21}V_2$.

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