

# Multicompartment Pharmacokinetic Models and Pharmacologic Effects

GERHARD LEVY, MILO GIBALDI, and WILLIAM J. JUSKO

**Abstract** □ The pharmacokinetic analysis of drug concentration in the plasma *versus* time data on the basis of multicompartment models makes it possible to examine not only the relationship between drug concentration in the plasma (or serum) and the intensity of a pharmacologic effect, but permits also an assessment of the relationship between pharmacologic effect and the relative drug levels in other apparent compartments of the body. Experimental difficulties such as sampling and assay problems limit the precision of data obtainable in the early (distributive) phase of drug concentration decline, so that most available data tend to fit a two-compartment rather than a more complex model. The rate constants derived from a two-compartment analysis of drug concentration data are almost certainly not "pure" but still hybrid, though "purer" than rate constants obtained by assuming the still simpler single-compartment open model. Suitable pharmacologic effect data, obtained at frequent intervals after drug administration, can show whether the site of action can be considered as part of a homogeneous tissue compartment (of the two-compartment system) or if the site of action must be considered as a distinct and separate pharmacokinetic compartment. This is illustrated by actual example, using previously published data of drug concentrations in the plasma and pharmacologic effects of lysergic acid diethylamide in man.

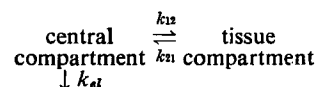
**Keyphrases** □ Pharmacokinetic models—pharmacologic effects □ Action-site relation—model compartment drug concentration □ Models, multicompartment—selection, data fitting □ LSD—pharmacokinetic analysis

Interest in the kinetics of drug absorption, distribution, and elimination has resulted in the development of many analytical and mathematical techniques which permit relatively sophisticated pharmacokinetic analyses (1). It is now frequently possible to characterize the distribution and elimination of a drug on the basis of two- or even three-compartment open models, and to calculate the relative drug concentrations in each of these compartments as a function of time. Similarly, clinical pharmacologic techniques have advanced to the point where it has become possible to make quantitative correlations between the intensity of certain pharmacologic effects and drug concentrations in plasma (or amounts of drug in the body). A number of these correlations have been shown to be consistent with basic pharmacokinetic principles (2, 3), and it has now become feasible to deal with even more complex systems such as the kinetics of apparently delayed pharmacologic effects (4). With a combination of precise and sufficiently frequent drug concentration and pharmacologic effect data, it should be possible to determine if the site of action of a drug is a pharmacokinetically indistinguishable part of one of the hypothetical compartments of the body (as determined for the particular drug), or if this site is in fact (part of) a distinctly separate pharmacokinetic compartment. Thus, suitable pharmacologic effect data may add another dimension to pharmacokinetic analyses by either indicating an association of

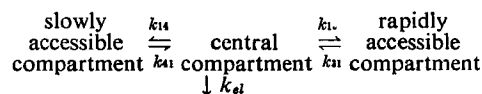
the site of action with one of the compartments evolved from the pharmacokinetic analysis of drug concentration data, or by suggesting the presence of a distinctly separate compartment—embodying the site of action of a drug—which is not readily discernible from the drug concentration data alone. It is the purpose of this communication to consider some of the relationships between the time course of pharmacologic effects and drug concentrations in the plasma and in other pharmacokinetically identifiable compartments of the body, and to show by actual example how a combination of drug concentration and pharmacologic activity data can be helpful (a) in the development of appropriate pharmacokinetic models; (b) in assessing the usefulness and limitations of pharmacokinetic analyses based only on drug concentration data; and (c) in obtaining a better understanding of the relationship of drug concentration in the plasma or serum and the intensity of pharmacologic effects. The example to be used is a pharmacologic effect (impairment of ability to solve mathematical problems) of lysergic acid diethylamide (LSD) in man, the intensity of this effect having been determined at frequent intervals after intravenous administration of the drug, concurrently with determinations of LSD concentrations in the plasma.

## METHODS

Plasma concentrations and pharmacologic effects of LSD following intravenous administration of 2 mcg./kg. body weight of the drug to five human subjects were obtained from Aghajanian and Bing (5). The plasma concentrations ( $C_p$ ) were given equal weight and were used as input data for the digital computer program of Marquardt (6) to provide a bi-exponential and tri-exponential least-squares regression fit to the data. The constants thus obtained were used as digital computer input along with the appropriate equations as described by Rescigno and Segre (7) to evaluate the rate constants and compartment drug levels of the two- and three-compartment open models (Models I and II).



Model I



Model II

## RESULTS AND DISCUSSION

A bi-exponential fit of the LSD-plasma-concentration data as a function of time ( $t$ ) yielded the following expression:

$$C_p = 5.469 e^{-7.815t} + 6.924 e^{-0.233t} \quad (\text{Eq. 1})$$

with a zero-time intercept of 12.39 ng./ml. ( $C_p^0$ ). The rate constants

obtained according to Model I are:

$$\begin{aligned} k_{el} &= 0.407 \text{ hr.}^{-1} \\ k_{12} &= 3.083 \text{ hr.}^{-1} \\ k_{21} &= 4.358 \text{ hr.}^{-1} \end{aligned}$$

Figure 1 shows the relative amounts of LSD in the central and tissue compartments as a function of time, calculated according to Model I. Shown also are the actual plasma concentrations divided by  $C_p^0$ , and the intensities of the pharmacologic effect at various times after drug administration. Comparison of the time course of pharmacologic effect and of drug levels in the central compartment shows that the site of action of LSD is apparently not located in the central compartment. Otherwise, the earliest measurement of pharmacologic effect would have been expected to yield the highest inhibition of normal performance (8). Can the site of action, therefore, be considered an indistinguishable part of the tissue compartment? This possibility can be tested by relating drug levels in the tissue compartment to the intensity of the pharmacologic effect. If a given tissue level yields essentially the same intensity of pharmacologic effect during the distributive phase (when tissue levels are rising) as during the period when tissue levels are declining, it can be concluded that the site of action is a pharmacokinetically indistinguishable part of the tissue compartment. Figure 2 shows the relationship between the fractional amount of LSD in the tissue compartment and the pharmacologic effect. It is readily apparent that data obtained during the early (distributive) phase do not show the same relationship between drug level and effect as data obtained during the period when tissue levels of LSD were declining. It should be noted that the deviation of the early data is not random but systematic in that the data converge with time on the response-log dose regression line obtained with the other data points. Thus, these data do not permit the conclusion that the site of action of LSD is an indistinguishable part of the tissue compartment. It appears that the site of action may in fact be (part of) a distinctly separate pharmacokinetic compartment.

A tri-exponential fit of the LSD-plasma-concentration data as a function of time yielded the expression:

$$C_p = 14.64 e^{-28.23t} + 2.016 e^{-2.484t} + 6.531 e^{-0.217t} \quad (\text{Eq. 2})$$

with a zero-time intercept of 23.19 ng./ml. The rate constants obtained according to Model II are:

$$\begin{aligned} k_{el} &= 0.738 \text{ hr.}^{-1} \\ k_{13} &= 14.54 \text{ hr.}^{-1} \\ k_{31} &= 10.21 \text{ hr.}^{-1} \\ k_{14} &= 1.565 \text{ hr.}^{-1} \\ k_{41} &= 1.879 \text{ hr.}^{-1} \end{aligned}$$

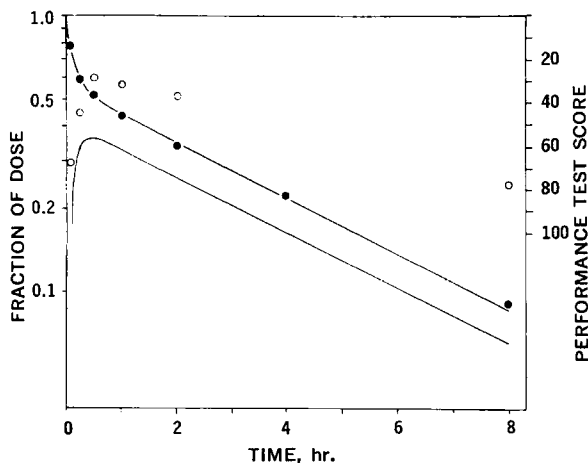


Figure 1—LSD in the central and tissue compartments as a function of time after intravenous administration of 2 mcg./kg.; average of five normal human subjects. Data analysis according to Model I. The upper and lower curves represent the central and tissue compartments, respectively. Closed circles are the relative plasma concentrations of LSD (i.e., the actual concentrations divided by the calculated zero-time concentration); the open circles are performance test scores (expressed as percent of normal performance in solving mathematical problems). Data from Reference 5.

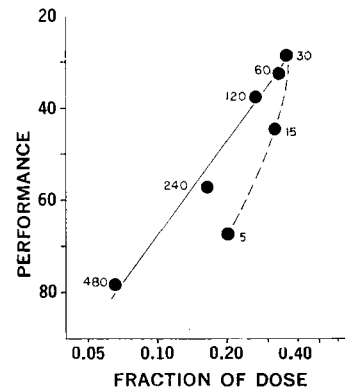


Figure 2—Relationship between the fractional amount of LSD in the tissue compartment of Model I and the intensity of the pharmacologic effect. The number next to each symbol represents the time in minutes when the measurements were made.

Figure 3 shows the relative amounts of LSD in the central, the rapidly accessible, and the slowly accessible compartments as a function of time, calculated according to Model II. Comparing Figs. 1 and 3 it appears that the experimental plasma level data fit very well to both Model I and Model II. The sum of the squared deviations of the observed from the calculated plasma concentrations is 0.003 on the basis of Model II, but 0.052 on the basis of Model I.

A plot of the intensity of pharmacologic effect versus the logarithm of the fractional amount of LSD in the rapidly accessible compartment of Model II shows a relationship similar to that depicted in Fig. 2. On the other hand, a similar plot with respect to the drug level in the slowly accessible compartment of Model II yields a straight line (Fig. 4). Unlike the case shown in Fig. 2, the data obtained in the distribution period fit very well on the regression line for all of the data points and give no evidence of a systematic deviation. The correlation coefficient of the data in Fig. 4 is 0.98. These observations suggest that the site of action of LSD is part of the slowly accessible compartment of Model II and show that Model I is insufficient to explain the total time course of LSD effects (9). The good correlation between the pharmacologic effect of LSD and the drug level in the slowly accessible compartment of Model II does not mean necessarily that the site of action of LSD and the slowly accessible compartment are identical. Rather, Model II is a better approximation of the biologic system than is Model I.

Berman (10), in reviewing the application of multicompartmental analysis to pharmacokinetics, pointed out that compartmental models are frequently a consequence of limited resolution in the

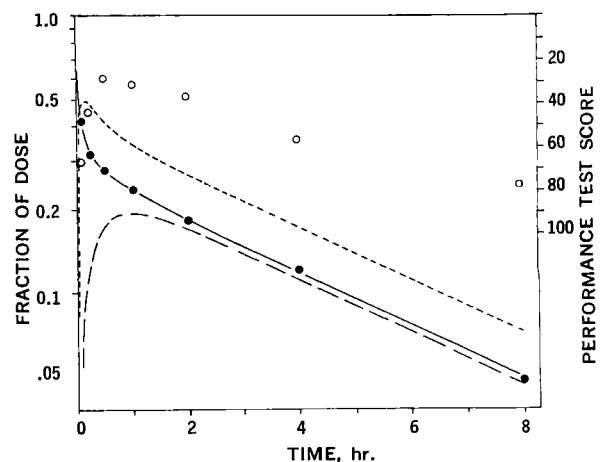


Figure 3—LSD in the central, rapidly accessible, and slowly accessible compartments as a function of time. Data analysis according to Model II. Key: ●, relative concentration of LSD in the plasma; ○, performance test scores; —, central compartment; ---, rapidly accessible compartment; - · -, slowly accessible compartment.

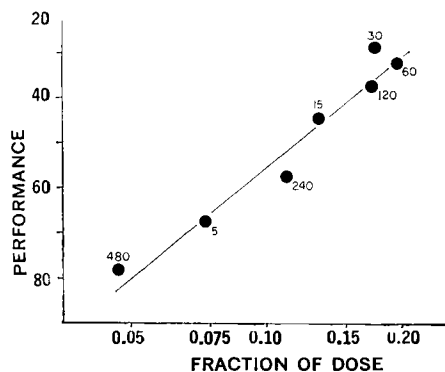


Figure 4—Relationship between the fractional amount of LSD in the slowly accessible compartment of Model II and the intensity of a pharmacologic effect. The number next to each symbol represents the time in minutes when the measurements were made.

data. He then stated that "In model building one starts with the simplest model consistent with known information, with preconceptions of the investigator, and with the data. New experiments are then designed to test the model further and to reveal new features about the system that are not contained in the model. The model is then modified to include the new information, and the process is repeated."

This is the approach that has been used here in that the pharmacologic activity data were used to test the two-compartment model (Model I), caused it to be rejected, and led to the three-compartment model (Model II) which is consistent with the available data. However, Model II is not the only three-compartment model which fits the data. For example, the data also fit to a three-compartment model (11) in which drug elimination occurs from the rapidly accessible compartment.

It is virtually impossible, in most instances, to distinguish between a two-compartment and more complex pharmacokinetic system on the basis of plasma concentrations alone. This difficulty is exemplified in the data shown in Fig. 5 which depicts the plasma concentration of LSD during the first hour and the theoretical curves related to Model I and Model II. The experimental data appear to fit each curve equally well. A distinction between the two curves could have been made only on the basis of experimental data obtained during the first two or three minutes after injection, providing that blood mixing problems would not have interfered. However, Wichmann *et al.* (12) have observed considerable fluctuation in the serum concentration of BSP during the first few minutes after intravenous injection of this drug, and attribute this to incomplete mixing of BSP in the blood. It is likely that this difficulty would be encountered also with other drugs.

It should be apparent, upon reflection, that any pharmacokinetic model is, by definition, a simplification of the real biologic system. In this context, it is to be regretted that a distinction has sometimes been made between "true" and "hybrid" rate constants when referring to the results of pharmacokinetic analyses based on two- and one-compartment models, respectively. The development of more detailed models simply results in increasingly closer approximation of the real biologic system. This process of refinement or purification may be thought of as being analogous to the successive processes of purification of an enzyme from its source.

It should be recognized that the pharmacokinetic analysis of the LSD data presented here has led to the development of a model which is consistent with the experimental data; this does not mean that the model is the correct one. There may be certain unrecognized factors, such as a possible delay in the pharmacologic effect of LSD relative to the time course of its concentration at the site of action, which could affect a theoretical analysis of the data. If and when such factors become evident, the model has to be revised. Many of the complexities of a pharmacokinetic analysis of pharmacologic

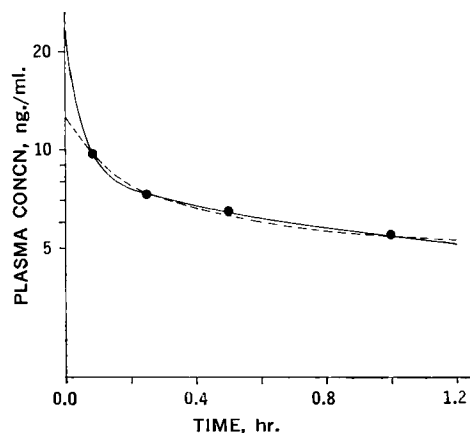


Figure 5—Concentrations of LSD in the plasma during the first hour after intravenous injection and the theoretical curves which are related to Model I (---) and Model II (—). Note that a distinction between these two curves can only be made in the first 2 to 3 min.

effects can be evaded by restricting the analysis to that time period when drug levels decline mono-exponentially,<sup>1</sup> since, as is evident in Fig. 3 and as has been shown theoretically (11, 13), the ratio of drug levels in each hypothetical compartment of the body is constant during this period. Examples of analyses of this type have been presented previously (2). While this paper has dealt specifically with a pharmacokinetic analysis of LSD data, it has been the intention of the authors to use the specific example to present principles which should be applicable whenever suitable drug concentration and pharmacologic effect data are available.

#### REFERENCES

- (1) E. R. Garrett, *Antibiot. Chemotherapia*, **12**, 227(1964).
- (2) G. Levy, *Clin. Pharmacol. Therap.*, **7**, 362(1966).
- (3) E. R. Garrett, A. J. Agren, and H. J. Lambert, *Intern. J. Clin. Pharm.*, **1**, 1(1967).
- (4) R. Nagashima, R. A. O'Reilly, and G. Levy, *Clin. Pharmacol. Therap.*, **10**, 22(1969).
- (5) G. K. Aghajanian and O. H. L. Bing, *ibid.* **5**, 611(1964).
- (6) D. W. Marquardt, "DPE-NLIN," Share General Library Program No. 7-1354.
- (7) A. Rescigno and G. Segre, "Drug and Tracer Kinetics," Blaisdell, Waltham, Mass., 1966, pp. 27-28, 93-94.
- (8) J. G. Wagner, G. K. Aghajanian, and O. H. L. Bing, *Clin. Pharmacol. Therap.*, **9**, 635(1968).
- (9) G. Levy, *ibid.*, **10**, 134(1969).
- (10) M. Berman, *Ann. Internal Med.*, **68**, 423(1968).
- (11) R. Nagashima, G. Levy, and R. A. O'Reilly, *J. Pharm. Sci.*, **57**, 1888(1968).
- (12) H. M. Wichmann, H. Rind, and E. Gladtko, *Zeit. Kinderheilk.*, **103**, 262(1968).
- (13) M. Gibaldi, R. Nagashima, and G. Levy, *J. Pharm. Sci.*, in press.

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<sup>1</sup> Pharmacokinetic models in which drug levels in the central compartment appear to decline mono-exponentially, but do not, will be considered in a subsequent communication.