Correlation of performance test scores with "tissue concentration" of lysergic acid diethylamide in human subjects

Previously published plasma concentrations of LSD-25, observed following intravenous injection of 2 mcg. per kilogram of LSD-25, have been found to be explained by the two-compartment open model. Performance scores on arithmetic tests were shown to be highly linearly correlated with the concentration in the "tissue" (outer) compartment. The estimated volume of the plasma (inner) compartment was 16.3 per cent of body weight, which is approximately the value reported for extracellular water; the estimated volume of the tissue compartment was 11.5 per cent of body weight. The estimated half-life for loss of LSD-25 from the plasma compartment, based on the model, was 103 minutes compared with a half-life of 180 minutes calculated directly from plasma concentrations.

John G. Wagner, Ph.D., George K. Aghajanian, M.D., and Oscar H. L. Bing, M.D.
Kalamazoo, Mich., New Haven, Conn., and Boston, Mass.
Clinical Pharmacology, Phase I, Medical Research Division, The Upjohn Company, Department of Psychiatry, Yale University School of Medicine, and Department of Internal Medicine, Tufts University School of Medicine

Aghajanian and Bing[1] administered 2 mcg. per kilogram doses of d-lysergic acid diethylamide (LSD-25) intravenously over a 1½ minute period to 5 volunteer male subjects. Blood samples drawn at 5, 15, 30, 60, 120, 240, and 480 minutes were heparinized and centrifuged. The separated plasma was analyzed for LSD-25 by a slight modification of the fluorometric method of Axelrod and co-workers.[2] After each blood sample was drawn, the subjects were given a series of equivalent simple arithmetic problems; these were to be solved as quickly as possible during a 3 minute period, and scores were expressed as a percentage of control values. The purpose of this report is to provide a mathematical analysis of the reported data on plasma concentrations in terms of a two-compartment open model.

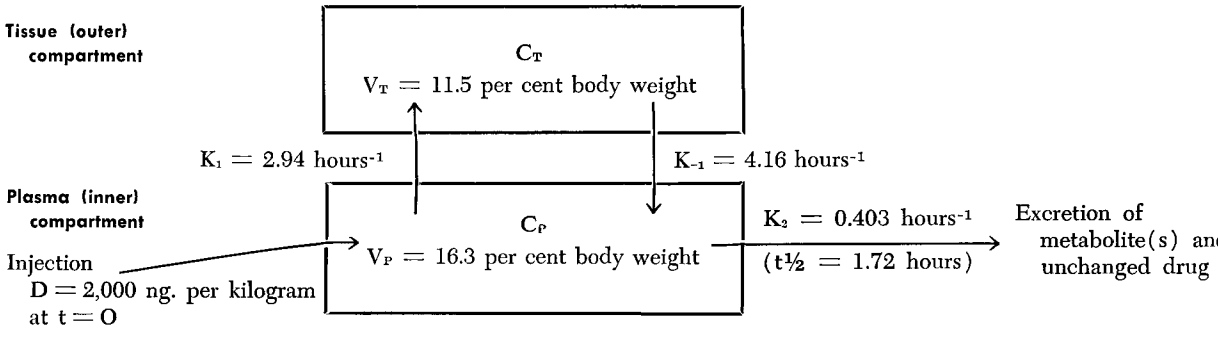
Received for publication Feb. 19, 1968.
Accepted for publication March 22, 1968.

Method

The equations (1 and 2) appropriate to the two-compartment model shown in Scheme 1 may be written as shown, where C_P is the concentration and V_P is the volume of the plasma or inner compartment, and C_T is the concentration and V_T is the volume of the tissue or outer compartment. D represents the administered dose and K_1 is the instantaneous fraction of drug being transferred from the inner to the outer compartment at time t. The other parameters are defined by equations 3 to 6, where K_2 is the first order rate constant for over-all loss of drug from the plasma compartment.

Equations 1 through 6, the average plasma concentrations of LSD-25 observed by Aghajanian and Bing,[1] preliminary graphic estimates of the parameters α, β, V_P, and K_{-1}, and D equal to 2,000 nanograms (ng.) per kilogram were used as input data for an IBM 360 computer program. The serum concentrations were given equal weights because of the small range of approximately 1 to 10 ng. per milliliter. The program of C. M. Metzler[5] and the IBM 360 System provided a least squares fit of the plasma concentrations appropriate to Equation 1. At the same time, the computer calculated the estimated values of the "tissue" concentration, C_T, corresponding to the blood sampling times, by use of Equation 2.

The average performance scores of Aghajanian and Bing[1] were then plotted against the estimated "tissue" concentrations for corresponding time values. The



Scheme 1. Compartment model for LSD-25 elaborated from plasma concentrations

$$C_P = \frac{D}{(\alpha-\beta)V_P}\left[(K_{-1}-\beta)e^{-\beta t} - (K_{-1}-\alpha)e^{-\alpha t}\right] \quad (1)$$

$$C_T = \frac{K_1 D}{(\alpha-\beta)V_T}\left[e^{-\beta t} - e^{-\alpha t}\right] \quad (2)$$

$$\alpha = \tfrac{1}{2}\left[(K_1 + K_2 + K_{-1}) + \sqrt{(K_1 + K_2 + K_{-1})^2 - 4\,K_{-1} \times K_2}\right] \quad (3)$$

$$\beta = \tfrac{1}{2}\left[(K_1 + K_2 + K_{-1}) - \sqrt{(K_1 + K_2 + K_{-1})^2 - 4\,K_{-1} \times K_2}\right] \quad (4)$$

$$K_{-1} = V\,K_1 \quad (5)$$

$$V = V_1\,V_2 \quad (6)$$

least squares regression line and the correlation coefficient were estimated.

Results

The compartment model elaborated* from the plasma concentration data is shown in Scheme 1.

Fig. 1 is a plot of the observed plasma concentrations; the dotted line drawn through these points is based on the least squares estimates. The solid dots in Fig. 1 are the estimated tissue concentrations, C_T, corresponding to the blood sampling times. The open circles in the figure are the average performance scores obtained at the same times. The sum of the squared observed plasma concentrations was 244, while the sum of the squared deviations of the estimated from the observed plasma concentrations was 0.048; hence the least squares line provided a very close fit to the observed data.

The inset in Fig. 1 is a plot of the average performance score against the estimated concentrations in the "tissue" (or outer) compartment. The least squares line for a linear regression is drawn through the points. The correlation coefficient was −0.940 ($0.01 > P > 0.001$). Hence there was a very high degree of correlation between the performance scores and the estimated "tissue" concentrations. The equation of

*The data of Axelrod and colleagues[2] support the model. In animals LSD is metabolized by the liver but not by other tissues. Hence LSD must enter the plasma compartment to be metabolized. They also found no blood brain barrier for LSD.

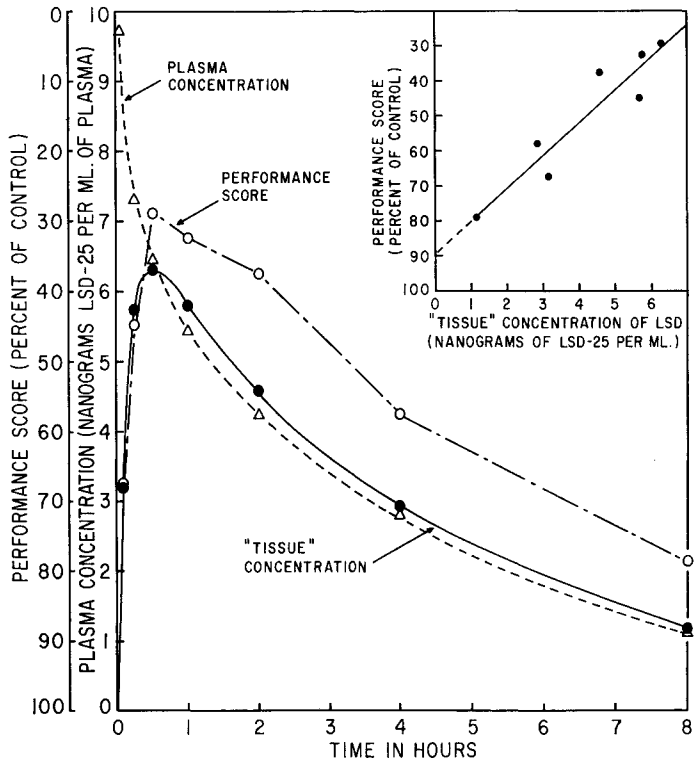


Fig. 1. Open diamonds are average plasma concentrations (C_P) of LSD-25 in 5 volunteers following intravenous injection of 2 mcg. per kilogram of LSD-25. Solid circles are predicted "tissue" concentrations of LSD-25 (C_T) based on the model shown in Scheme 1, which was derived from the plasma concentrations. Open circles are average performance scores in arithmetic tests. Inset shows plot of average performance score against "tissue" concentration of LSD-25.

the least squares line in the inset figure is as follows:

$$S = 89.7 - 9.44\ C_T \qquad (7)$$

where S is the average performance score expressed as a per cent and C_T is the estimated "tissue" concentration of LSD-25 in nanograms per milliliter.

The value of β, calculated by means of Equation 4, is 0.231 hour^{-1}, corresponding to a half-life of 180 minutes. Hence this half-life agrees with the value of 175 minutes originally estimated from the plasma concentration directly by Aghajanian and Bing.[1] A plot of the logarithm (base e) of the estimated total amount of drug in the body at time t (i.e., $C_1V_1 + C_2V_2$) against time yields the same rate constant and half-life. Hence this may be considered to be the "biological half-life" of LSD-25. However, the rate constant for loss of LSD-25 from the inner (plasma) compartment of the model is 0.403 hour^{-1}, which corresponds to a half-life of 1.72 hours. This situation has been discussed by Wagner and Northam.[6]

The estimated volume of the inner compartment was 0.163 L. per kilogram, 16.3 per cent of body weight. This volume is within the range of the values reported by Deane[3] for extracellular water in man. The estimated volume of the outer compartment was 0.155 L. per kilogram or 11.5 per cent of body weight. Hence the total apparent volume of distribution of LSD-25 was 27.8 per cent of body weight.

Discussion

Since LSD principally affects mental function, it is logical to expect that the concentration of LSD in the cerebrospinal fluid and the brain would determine the intensity of its pharmacologic effect(s). The higher the brain concentrations of LSD, the lower one would expect the performance score to be. The results reported support such a direct proportionality, if one assumes that the "tissue" concentration, estimated by use of the model, is equal to, or directly proportional to, the brain level of LSD.

This interpretation of the data of Aghajanian and Bing[1] is considerably different from the interpretation made by Levy.[4] Levy's interpretation involved two questionable assumptions. First, he assumed that the plasma concentrations of LSD after intravenous administration could be described by a single exponential component; however, his graph showed this was not so, since his regression line fitted only 4 of the 7 plasma concentrations. Secondly, Levy assumed that the performance scores were proportional to the logarithm of the plasma concentrations of LSD. Even in cases where response is related to plasma concentration, the relationship of response to the logarithm of the plasma concentration is an approximation valid in the 20 to 80 per cent response range, but invalid in the 0 to 20 and 80 to 100 per cent response ranges. In the LSD case, the approximation holds for only 5 of the 7 performance scores, and is a consequence of the approximate parallelism between C_P and C_T from 0.5 to 8 hours, as indicated in Fig. 1. Hence our interpretation made use of all the data points, whereas Levy's interpretation made use of only selected points.

We wish to thank Dr. C. M. Metzler of the Mathematical Services, Information Systems and Computer Services, The Upjohn Company, for providing the nonlinear least squares estimates.

References

1. Aghajanian, G. K., and Bing, O. H. L.: Persistence of lysergic acid diethylamide in the plasma of human subjects, CLIN. PHARMACOL. & THERAP. **5**:611-614, 1964.
2. Axelrod, J., Brody, R. O., Withop, B., and Evarts, E. V.: The distribution and metabolism of lysergic acid diethylamide, Ann. New York Acad. Sc. **66**:435-444, 1957.
3. Deane, N.: Intracellular water in man, J. Clin. Invest. **30**:1469-1470, 1951.
4. Levy, G.: Kinetics of pharmacologic effects, CLIN. PHARMACOL. & THERAP. **7**:362-372, 1966.
5. Metzler, C. M.: Personal communication.
6. Wagner, J. G., and Northam, J. I.: Estimation of volume of distribution and half-life of a compound after rapid intravenous injection, J. Pharm. Sc. **56**:529-531, 1967.