Correspondence

A mathematical model for the pharmacokinetics of LSD effect

To the Editor:

When properly used, mathematical models not only describe the pharmacokinetics of a drug, but can also provide additional insight and suggest future experiments. In the September-October, 1968, issue of this JOURNAL, Wagner and associates[7] proposed a two-compartment open model for the plasma concentration and pharmacologic effects of d-lysergic acid diethylamide (LSD-25) in man. They then used this model to conclude that the relation of "tissue" concentration to performance scores on an arithmetic test was linear. In a later communication,[4] Levy, whose earlier proposal[3] that the logarithm of plasma concentration and performance was linear was criticized by Wagner and associates,[7] pointed out that the model used by Wagner and associates[7] did not seem to fit the data over the entire time span of the experiment.

It can be demonstrated that: (1) If all the experimental information is used to estimate the parameters of the model proposed by Wagner and associates,[7] then the model does agree well with the data over the entire time of the experiment. (2) Thus, it is in general not necessary to restrict pharmacokinetic models to the "so-called β-phase" of an experiment. (3) The data of the LSD-25 study by Aghajanian and Bing[2] do not contain enough information to reject either the linear or the log-linear relationship between "tissue" concentration and performance.

With the use of the model and notation of Wagner and associates,[7] the concentrations of LSD-25 in the plasma and "tissue" compartments are $C_P(t)$ and $C_T(t)$, respectively, and the performance score on the arithmetic problems is $S(t)$. An assumed linear relation between "tissue" concentration and performance can be expressed as:

$$S(t) = 100. - F_1 \times C_T(t). \qquad (1)$$

An assumed linear relation between the logarithm of "tissue" concentration and performance is expressed as:

$$S(t) = 100. - F_2 \times \log C_T(t), \text{ where } F_1 > 0. \qquad (2)$$

(Both equations have certain theoretical difficulties if applied over too wide a range, since Equation 1 implies that a large concentration would result in negative performance scores and Equation 2 implies that concentrations less than unity improve performance.)

With the use of either Equation 1 or Equation 2, the LSD-25 data provide direct observations of the plasma compartment and indirect observations of the "tissue" compartment of the model, and all of the data can be used to estimate the rate constants K_1 and K_2, the volumes V_P and V_T, and the factor F. Unfortunately, Wagner and associates[7] used only the plasma concentration data $C_P(t)$ to estimate the rate constants and volumes; with these estimates they predicted "tissue" concentrations from the model. Finally they estimated F by correlating the observed performance scores and the predicted "tissue" concentrations. Since partial information may result in biased estimation, it appeared that the model, as evaluated from their Fig. 1,[7] did not agree well with

Table I. *Plasma concentrations of LSD-25 (ng./ml.), performance scores (% control), and predicted "tissue" concentrations (ng./ml.)*

Subject	*5 min.*	*15 min.*	*30 min.*	*1 hr.*	*2 hr.*	*4 hr.*	*8 hr.*
1	11.1	7.4	6.3	6.9	5.0	3.1	0.8
	72	55	74	81	79	89	106
	7.11	7.89	7.41	6.48	4.96	2.90	0.99
2	10.6	7.6	7.0	4.8	2.8	2.5	2.0
	73	60	35	50	48	73	97
	2.19	4.07	5.15	5.21	4.16	2.54	0.94
3	8.7	6.7	5.9	4.3	4.4	—	0.3
	60	23	6	0	27	69	81
	2.25	4.17	5.22	5.17	3.95	2.21	0.69
4	10.9	8.2	7.9	6.6	5.3	3.8	1.2
	60	20	3	5	3	20	62
	2.43	4.60	5.98	6.36	5.64	4.24	2.39
5	6.4	6.3	5.1	4.3	3.4	1.9	0.7
	78	65	27	30	35	43	51
	0.97	2.00	2.88	3.49	3.41	2.80	1.86
Average	9.54	7.34	6.44	5.38	4.18	2.82	1.00
	68.6	44.6	29.0	33.2	38.4	58.8	79.4
	2.39	4.35	5.41	5.47	4.59	3.13	1.46

For each subject the numbers are plasma concentration, performance, and predicted "tissue" concentration, respectively. For the average, the plasma concentration and performance are averages of the 5 subjects; the "tissue" concentration is predicted from these averages by the model. The predicted "tissue" concentrations were obtained with the use of Equation 1.

Table II. *Correlations between observed and model predicted values of plasma concentration and performance scores*

	Linear (Eq. 1)		*Linear-log (Eq. 2)*	
Subject	*Plasma concentration*	*Performance*	*Plasma concentration*	*Performance*
1	0.990	0.915	0.989	0.897
2	0.979	0.955	0.979	0.953
3	0.984	0.987	0.988	0.926
4	0.988	0.972	0.990	0.992
5	0.965	0.918	0.964	0.909
Average	0.998	0.995	0.998	0.985

the data obtained in the early part of the experiment.

For each subject tested by Aghajanian and Bing[2] there are 7 pairs of observations, each pair of observations being a plasma concentration and a performance score. The 35 pairs of observations as furnished by Aghajanian[1] are given in Table I. For each subject, individually, and for the average values, a computer program[5] was used to fit the model to all the observations (14 data points) for the experiment.* The adequacy of the model may be judged by how well the predicted values correlate with the observed values.

*For the weighted least-squares fitting, the deviations from plasma concentrations and from performance scores were assigned weights of 1.0 and 0.01, respectively, in order to give all observations approximately equal influence on the fit.

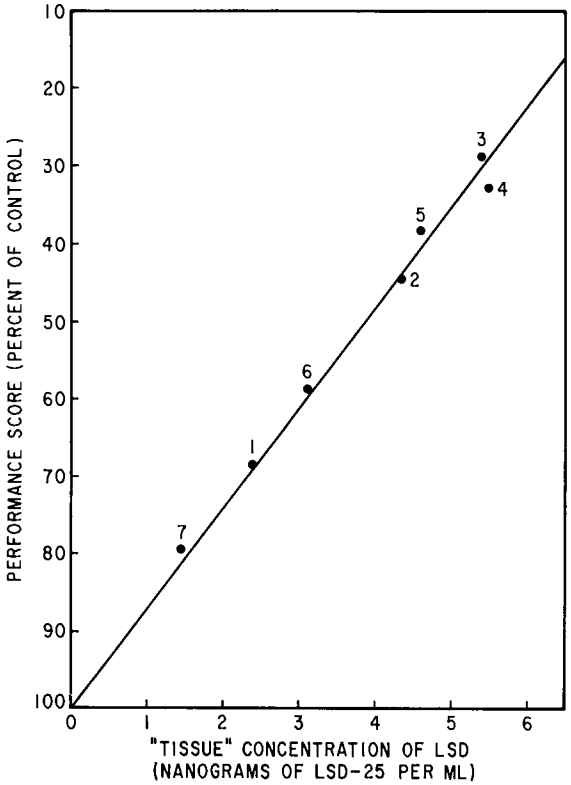

Fig. 1.

In Table II are the correlations between observed and predicted plasma concentrations and between observed and predicted performance scores with the use of either Equation 1 or Equation 2. It can be seen that with either assumed relation the correlations are all high, and for the average values the correlations between observed and predicted performance scores are 0.995 (assuming linear relation) and 0.985 (assuming log-linear relation). These correlations are also the correlations between predicted "tissue" concentration and observed performance for which Wagner and associates[7] obtained a correlation of 0.940 and Levy,[4] with the use of "data only from the β-phase" obtained "about 0.99." Fig. 1, which corresponds to Fig. 1 of Wagner and associates[7] and also to Fig. 1 of Levy,[4] shows that the model agrees well with all the data. Plots of the 5 individual subjects' values, as given in Table I, show the same good agreement over time, although there is more scatter in the data.

This excellent agreement of the model and data does not prove that "the site of action of LSD is a pharmacokinetically indistinguishable part of their hypothetical tissue compartment,"[4] since it may be that the site of action is in a third compartment where the concentration has a high correlation with the concentration of the "tissue" compartment, i.e., rapid exchange between the two. But the excellent fit of the model to the data refutes the statement that "the data indicate that the site of action of LSD must be treated as a separate compartment entirely."[4]

Thus, it has been demonstrated that: (1) With improved estimation of parameters, the model proposed by Wagner and associates[7] does agree well with all the data. (2) With the proper mathematical tools it is possible to construct models which describe an entire pharmacokinetic experiment and not just the "so-called β-phase." (3) From the information contained in the LSD-25 data, the relation between performance and "tissue" concentration of LSD-25 could be either linear or log-linear (but may be neither).

One additional point: Levy[4] refers to Riggs[6] in support of the "linear-logarithmic" relationship. Riggs, in the cited reference, only says that plotting the relationship on semilog plotting paper produces "a symmetrical sigmoid curve whose midportion approximates a straight line,"[6] which is not quite the same as "a sound theoretical and well-accepted basis for the latter type of relationship."[4]

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Reply

To the Editor:

Metzler and others interested in the relationship between LSD concentration and pharmacologic effect may wish to read our recent paper[3] in which this relationship is analyzed and discussed in terms of both two-compartment and three-compartment pharmacokinetic models. In addition, I offer the following specific comments with respect to Metzler's communication[4]:

1. Metzler[4] and I[2] agree that the LSD data are not suitable for distinguishing between a linear and linear-logarithmic correlation of effect and drug concentration, while Wagner[6] evidently did not consider this possibility.

2. Metzler[4] assumes a priori either a linear or linear-logarithmic relationship between effect and concentration and determined the pharmacokinetic rate constants and volumes on the basis of both the concentration and effect data. This procedure yields automatically a better correlation between the theoretical tissue concentration and effect values. We[3] made no such assumption but rather calculated the theoretical tissue levels of LSD from the plasma concentrations only and then tested various kinds of correlation. By this approach we found a very good correlation between theoretical tissue levels and LSD effects when the theoretical tissue levels were obtained on the basis of a three-compartment pharmacokinetic model. The two-compartment model used by Wagner[6] did not yield a satisfactory correlation.[2, 3]

3. As Metzler,[4] but without using the LSD effect data to "help" in obtaining appropriate pharmacokinetic constants, we have demonstrated a very good correlation of *all* the concentration and effect data, i.e., not only in the β-phase.[3] Metzler apparently was not aware of our paper when he wrote his communication.

4. There is a sound theoretical and well-accepted basis for the linear-logarithmic sigmoid effect-concentration relationship analogous to the Langmuir adsorption isotherm,[1] and it is recognized[5] that the mid-portion of this curve approximates a straight line. We therefore chose to plot our data in this manner.

5. For those specifically interested in the pharmacology of LSD rather than in pharmacokinetics per se, it must be pointed out that the pronounced variability of the individual data (as seen in Metzler's table, these individual values were not available to me up to now) hardly justifies an extensive rigorous pharmacokinetic analysis. As we have already pointed out elsewhere,[3] such an analysis is useful primarily for developing general concepts in pharmacokinetics, and Metzler's communication[4] is to be welcomed in this context.

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Sample size

To the Editor:

I should like to comment on the article, "Sample size in psychiatric drug research," by Karl Rickels and Blaine E. McLaughlin which appeared in the September-October, 1968, issue of CLINICAL PHARMACOLOGY AND THERAPEUTICS—and to ask for Dr. Donald Mainland's comments on my comment.

The authors' final remarks, ". . . in . . . trials . . . in which variability of patient response represents the major source of experimental error, small samples are no longer defensible," are direct and to the point. I agree with them. However, I must disagree with the data handling and analysis.

They really did two experiments—and not one—and having computed significance levels in the first experiment (Sample A), formal statistical procedures do not permit their lumping these data with later data and doing another significance test. The error (of making significance tests at a fixed level until "significance" is reached) is one which the writers on sequential experimental procedures specifically warn against (e.g., Armitage, *Quarterly Journal of Medicine* 23:255-274, 1954).

Since these were two experiments, I broke down the data by the two time periods in which they were collected. (Table I). Where enough data were given I estimated standard errors. The second part now looks rather different from the first. Five of the 6 average scores in the second part were lower than those in the first part. (I assume that the "total" is made up of the other two—so it might be better to say 3 out of 4 are lower.) The sixth score is the same. In one of the pair of scores, somatic cluster, placebo, the difference between experiments may be large enough to be statistically significant. And finally, the first part of the experiment attempted to assign patients on a 1:1 basis (drug:placebo), and the second part assigned them 2:1.

Modern statistical theorists hold that an experimenter should conduct an experiment any way he pleases—and stop whenever he wishes. If he wants to change from

Table I

		Mean scores					
		Total "B"		*First part "A"*		*Second part "B"-"A"*	
Measure	*Treatment*	*N*	$\bar{X}$	*N*	$\bar{X}$	*N*	$\bar{X}$
Emotional cluster	Drug	69	2.78±.09	35	2.92±.12	34	2.64±.12
	Placebo	56	3.21±.10	39	3.21±.12	17	3.21±.17
Somatic cluster	Drug		2.51		2.69		2.32
	Placebo		2.86		3.05		2.42
Total score	Drug		2.64		2.79		2.49
	Placebo		3.03		3.14		2.78

a 1:1 ratio to a 2:1 ratio, that's his business. He just has to handle his data appropriately. Mostly the experimenters should compute likelihood ratios and not significance levels.

If one is going to be more traditional, then one can follow R. A. Fisher's suggestions on how to combine results from separate experiments.

$$(\text{Compute} - \sum_{1}^{} 2 \log_e p_i,$$

where p_i is the probability level computed in each of the i experiments, through standard techniques. This sum is distributed like χ^2 with 2i degrees of freedom. Say, for example, for "emotional cluster," p for the first experiment was about 0.1 and for the second was 0.05.

Then $\chi^2 = \sum^{2} - 2lnp = 4.606 + 5.993 =$ 10.598, which for 4 degrees of freedom is significant at the 0.05 level.)

Another way of going about this might have been to set up a (closed) sequential t test, and then make pair-wise comparison of drug and placebo patients, ending the trial when one of the sequential t boundaries was crossed. This imposes an arbitrary stopping rule (the boundaries of the sequential t), to which some modern statisticians object, but it does allow the investigator to end the trial at the earliest time at which he can make a significance statement.

Summary? Statistical techniques appropriate to the way the data are collected should be used.

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Reply

To the Editor:

Mea culpa! When I first read the manuscript I saw some statements in the text that required elucidation, but I did not scrutinize the details of the analysis and observe the fault that Dr. Schneiderman has pointed out. When the authors made the suggested changes I passed the manuscript for publication, still without scrutinizing the numerical part. In a manuscript that presents a general idea or fact that seems important, rather than a specific finding in an experiment, I am perhaps too careless about figures. Even in the more specific reports, and even if sufficient data are available, I have not the time to test much of the analysis. It is therefore gratifying, and may be salutary to contributors, to know that expert eyes often scrutinize their quantitative work after it has been printed.

Dr. Schneiderman has neatly presented alternative games that theorists offer to investigators; but has very rightly indicated that, having chosen a particular game, an investigator must abide by its rules. Many of them may regret that they have no criteria to guide them in their choice, and that when the game is over they do not really know what the results mean.

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