*Br. J. Pharmac.* (1973), **49**, 328–339.

# Lithium kinetics in man: effect of variation in dosage pattern

P-E. E. BERGNER, K. BERNIKER,* T. B. COOPER, J. R. GRADIJAN AND G. M. SIMPSON

*Research Center, Rockland State Hospital, Orangeburg, New York, U.S.A. and * Massachusetts Institute of Technology, Cambridge, Massachusetts, U.S.A.*

**Summary**

1. Utilizing a general stochastic theory of drug kinetics we have demonstrated that from the serum concentration curve derived from a single dose of lithium, it is possible to predict the steady state concentration, the time required to reach steady state, the dependency of these quantities on the time interval between drug administrations and the fluctuations in plasma level under steady state conditions.

2. It has been shown in general that the more frequently the drug is administered the higher is the steady state level, the shorter is the time required to reach steady state, and the smaller are the fluctuations.

## Introduction

The significance of serum levels of drugs used in psychopharmacology is still a subject of controversy. It is only recently that methods have become available which enable us to measure the plasma levels of many such drugs with relative ease. Despite the argument that the plasma level may merely reflect the degree of absorption of a compound from the site of administration (Whelan & McFadzean, 1964), in the field of psychopharmacology evidence is accumulating which would indicate that the therapeutic outcome may well be dependent upon the drug plasma level (Curry, Marshall, Davis & Janowsky, 1970; Hammer, Idestrom & Sjoqvist, 1967; Levine, Clark & Manian, 1969; Sjoqvist, Hammer, Idestrom, Lind, Tuck & Asberg (1968). In a review of the literature Cash & Quinn (1970) conclude that 'it would appear that the therapeutic response to a drug is dependent upon the plasma level of the drug which in turn is regulated by metabolic processes'. From this it follows that only that patient with the average amount of drug metabolizing enzyme available will benefit from the standard drug therapy. Those patients at each tail of the distribution of plasma levels will either accumulate to toxic levels or never achieve a therapeutic level. If the therapeutic blood level can be established and the patient's drug metabolizing capacity determined, then a drug regimen could be determined giving the optimal therapeutic level for that patient.

Lithium in the treatment of mania is a unique substance in that it does not have any metabolites, it is very easily measured in plasma or other tissues and treatment is controlled by measuring blood levels. The blood level is measured primarily because of toxic side effects and dangers which may ensue if the patient's level

exceeds 2·0 mEq/litre. There is a great deal of evidence to show that the maintenance dose to achieve steady state of ca 1·0 mEq/litre varies considerably from patient to patient from 600 mg per day to in excess of 4 gm per day. Because the relation between plasma level and dose regimen varies from one patient to another it would be helpful if a method could be found that without time delay informs the clinician about the patient's individual dose requirements.

The basic question to be considered in this investigation is the followng: Assume that the patient is given a single dose at time zero of a prospective drug and that the plasma concentration is recorded at discrete time points following administration. Would it then be possible to estimate, from such observations, the plasma level that would eventually be obtained after a regular regimen is started?

Questions of this type have already been discussed in the literature (e.g. Wagner, Northam, Always & Carpenter, 1965) and the kinetic equations are equivalent to those we shall apply. However, the equations can be given a more general physico-mathematical basis, previously worked out for tracer kinetics (cf. Bergner, 1961, 1964). In that approach, the metabolic system is represented in abstract probability terms, not to account for statistical fluctuations, but to allow a uniform representation of arbitrarily complex physico-chemical processes; e.g. it is not necessary to introduce such biologically questionable concepts as homogeneous compartments. Thus the equations' validity and informative value are extended.

We shall show that a clinically feasible method can be designed that reasonably will predict individual plasma levels of lithium and, moreover, that one can gain some insight as to how patients differ in plasma level responses to variations in dose regimen.

*Mathematical considerations*

Consider a single dose M (grams, moles) of a drug given to a subject at time t=0. Let m(t) be the amount of the drug found in a blood sample at time t due to this dose. Now assume that a regular drug regimen is begun such that the dose M is given repeatedly every $\tau$ time units. Provided the system is 'stationary' and 'linear' (these conditions are discussed below), it is well known that the amount of drug one would find in a blood sample taken immediately before the (n+1)th dose can be expressed by

$$A(n\tau)=\sum_{j=0}^{n} m(n\tau) \qquad \text{Eq. 1}$$

Furthermore, if the system is "open" (Bergner, 1967), i.e. particles entering the system remain only a finite time, the steady-state amount

$$A_s(\tau)\equiv\lim_{n\to\infty} A(n\tau) \qquad \text{Eq. 2}$$

exists and is finite. Hence, under these conditions, it follows that the steady-state amount of drug in plasma can be predicted from a single-dose study. However, since the basic assumptions of stationarity and linearity are essential, we shall now briefly discuss the implications of these conditions.

A system is said to be stationary if the response to a given dose does not depend on the time that dose is given. A system is said to be linear if the response to two separate inputs is the sum of the individual responses to the two inputs.

(This is the classic concept of superposition. Zadeh (1962) has suggested a more extensive definition of linearity that includes systems not satisfying the superposition condition.) Equation 1 requires that both these conditions be valid for any enumerable sequence of inputs.

In physico-chemical terms, linearity implies that the drug molecules are mutually independent. Physical independence in this sense implies, moreover, that the drug itself cannot cause any departure from stationarity. In other words, if linearity holds it is necessary that stationarity hold as well, unless there are some *non-drug factors* causing departure from stationarity; examples of such possible factors are dietetic variations, change in clinical status and aging. This means that if we can exclude that kind of disturbance, any experimentally observable violation of Eq. 1 must be ascribed to interaction between drug molecules.

What are the possible types of interactions between drug molecules? An obvious one would be direct collisions. However, most drugs are administered in such small amounts relative to the volume of distribution that the probability for collisions to occur must be negligible.

More likely, then, is an *indirect particle interaction* caused by a systemic response to the drug, and a subsequent change in drug metabolism. In terms of the present concepts we can easily visualize such a situation: some of the molecules in the first dose hit a certain 'target', thereby inducing catabolic enzymes that increase the metabolic breakdown of the drug; other examples are hormonal and C.N.S. responses causing, say, changes in the renal excretion. Hence, when another dose is given later, the metabolism of its molecules will differ from the one they would experience had no drug been supplied previously; i.e. linearity does not hold.

This means that, even when the approach fails to predict the steady state concentration, it may still provide valuable information about the metabolism: as we have just concluded, if external factors can be ruled out, about the only thing to suspect is indirect interaction between the drug molecules as the reason for failure. We have, thus, been able to limit the number of possibilities to essentially one, which is because Eq. 1 is derived under liberal conditions; apart from linearity and stationarity there are no substantial constraints on the system. Thus, there are no restrictions regarding the system's complexity: there may be endless assortments of protein bindings, diffusions in and out of cells and slow dilutions into various parts of the extravascular space. Moreover, the non-drug composition (e.g. cells and proteins) of the blood samples is arbitrary as long as it does not vary from sample to sample.

The reason for stressing these features of the theory is that, in pharmacokinetics, the dominating approach for derivation of Eq. 1 has been so-called compartment analysis (e.g. Wells, 1954; Rossum & Tomey, 1970), which perhaps is quite natural as this methodology seems to have originated within pharmacology (Theorell, 1937). However, since World War II, the main activity in this kind of biokinetics has rather been in tracer kinetics where compartment analysis has not only been heavily employed but also criticized (the book edited by Bergner & Lushbaugh, 1967, gives a review of the conflicting viewpoints). The main objection to compartment analysis has been that it oversimplifies the biological system and that, therefore, the validity of equations based on this approach might be quite limited.

It means, for instance, that if a relation like Eq. 1 fails empirically, one would have to question not only the linearity (or, independency) condition but also the very model on which the equation is based.

The concept of steady state is somewhat ambiguous as is also the terminology surrounding it. When a regular drug regimen is started one should expect that, when $\tau > 0$, the plasma drug level will show a wave-like behaviour as illustrated by Fig. 1: between consecutive doses the level assumes a highest and lowest

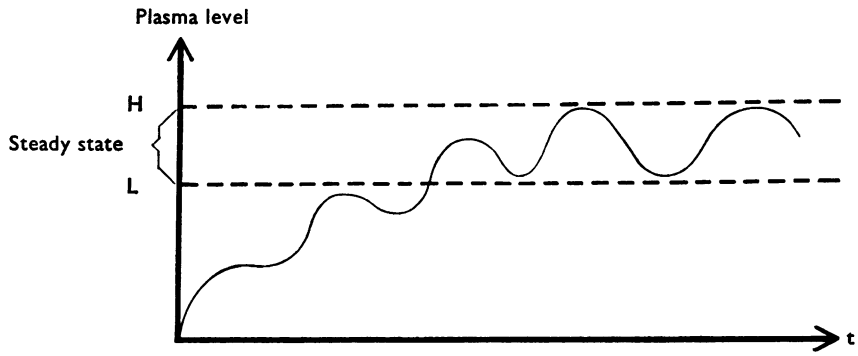


FIG. 1. The behaviour one should expect of the plasma concentration curve when a regular regimen is started. The time-distance between consecutive minima is equal to the time interval between medications.

value. We shall here accept as a definition that steady state is obtained when these two plasma levels remain invariant from one $\tau$-interval to another. Phrased differently, the high and low plasma levels are our two state variables, and the system is said to be in steady state when these variables are time invariant. An alternative term appearing in the literature is stationary state, whereas in our opinion the label 'equilibrium' should not be used because of the precise and specific significance given to it in physics (cf. Prigogine, 1955).

But what does the quantity $A^s(\tau)$ defined by Eq. 2 then represent? For oral drug administration,

$$A^s(\tau) = L(\tau) \qquad \text{Eq. 3}$$

where the meaning of L is shown by Fig. 1: the lowest value assumed by the steady state plasma level immediately before a new dose is given (oral administration).

To complete the mathematical theory, the final problem to be solved is to give m(t) an experimentally workable parametric form (actually, this is not absolutely necessary but simplifies the data and mathematical analysis). Due to the noncompartment approach we are free to choose any form that

1) is integrable over $(0, \infty)$
2) satisfies $\int_0^\infty m(t)\,dt < \infty$
3) gives good data fit

Nevertheless, we shall in this investigation assume the classic form

$$m(t) = \sum_{i=1}^{r} \beta_i e^{-\alpha_i t} \qquad \text{Eq. 4}$$

$0 < \alpha_1 < \alpha_2 \ldots < \alpha_r$

not because of a specific model but of the common experience that kinetic data of this type are often representable by such functions which, moreover, are mathematically and numerically convenient. Thus, Eq. 4 gives, together with Eqs. 1, 2 and 3,

$$L(\tau)=\sum_{i=1}^{r} \frac{\beta_i}{1-e^{-\alpha_i \tau}} \qquad \text{Eq. 5}$$

This equation, or its equivalent, has appeared for a long time in pharmacokinetics (cf. Wells, 1954; Kruger-Thiemer, 1960) and has been applied by, for instance, Hammer & Brodie (1967).

Experimental Design:

Consider the situation where a patient is given a single oral dose M at the time $t=0$, and that m(t) is observed at the instances $t_1, t_2, \ldots, t_n$. After $t=t_n$ a regular drug regimen is started (i.e. the dose M is given at instances $\tau$ units apart) and later, when steady state should theoretically be achieved (see below), the plasma drug level is recorded immediately before the next dose is to be given.

This last observation gives us the *recorded L-value*, which we donate by $L^r(\tau)$. If m(t) is sufficiently often and accurately observed, it should be possible to estimate the $\alpha$'s and $\beta$'s in Eq. 5, and thereby obtain a predicted L-value, denoted by $L^p(\tau)$. When the difference

$$\triangle L \equiv |L^p(\tau)-L^r(\tau)|$$

is small, we conclude that the system is linear and stationary, and the initial single-dose procedure may then be used for the design of therapeutic dose regimens in individual patients. On the other hand, should $\triangle L$ prove large we conclude, according to the previous section, that there is an indirect particle interaction which, in the following, we shall call *adaptation*.

What is a small (or, large) value of $\triangle L$? No definite answer exists, but must be decided upon from a practical point of view. We may, for instance, apply the rule that $\triangle L$ is small when, empirically, $L^p$ proves to be a clinically useful predictor to $L^r$. This means then that when for one drug $L^r$ must be kept within narrow limits for therapeutic effects without toxic reactions, a 'small value of $\triangle L$' is less than for a drug where these limits are less critical.

To complicate things further, a true steady state is hardly ever obtained: in one subject, $L^r$ may vary from day to day, and may also depend on when during the day it is observed. Moreover, for a given set of m(t) data—from now on referred to as the kinetics—different values of $L^p$ can often be obtained, depending on what numerical method is used for estimating the $\alpha$'s and $\beta$'s. Whereas there is not much one can do about the variation in $L^r$, the uncertainty in $L^p$ is, in principle, possible to deal with, e.g. by selecting different numerical procedures.

The purpose of the type of experimental scheme outlined above would be to see whether given kinetics (i.e. choice of $t_1, t_2, \ldots, t_n$) and a given numerical procedure lead to a small $\Delta L$. For clinical reasons, the choice of kinetics is usually quite limited; in this investigation we concluded that n should be less than 9 and that $t_n \leqslant 24$ hours. More precisely, as a general rule we have throughout used (hours) $t_1=0{\cdot}5$, $t_2=1{\cdot}0$, $t_3=2{\cdot}0$, $t_4=3{\cdot}0$, $t_5=4{\cdot}0$, $t_6=6{\cdot}0$, $t_7=8{\cdot}0$, $t_8=24{\cdot}0$. Of course, for practical reasons the actual time points where blood samples were taken had a

spread of approximately 5 min around these values. Because m(0)=0 for oral administration, this gives altogether 9 m(t) values.

The next step in the experimental design is to select a value of r in Eq. 5, and we have here chosen r=3. The reason for not selecting a larger r value is recent findings indicating that the statistical errors in the $\alpha$ and $\beta$ estimates increase extremely fast with r (Bergner, Takeuchi & Lui, 1973).

When it comes to the actual curve fitting which defines the $\alpha$ and $\beta$ estimators, we considered curve peeling, and iterative estimation, and selected the former as the basis for the computer procedure. The motivation for this choice is that we avoid problems involved with the iterative procedure regarding the selection of starting values for the $\alpha$'s and $\beta$'s.

However, no matter what mathematical form of m(t) is chosen, or what kind of numerical parameter estimation is used, the kinetics to work with consists of only nine, somewhat scattered, points and, therefore, some sort of 'data smoothing' is needed. Of all various possibilities we have selected the oldest and simplest one, namely to draw free-hand a smooth curve through the data points; Myhill, Wadsworth & Brownell (1965) discuss an alternative, more formal procedure. The curve thus obtained is here referred to as the *interpretation*, reflecting the fact that it is a realization of the investigator's subjective feeling of what the curve would look like had the plasma level been continuously recorded without errors. It is in our opinion an open question whether our approach is more subjective than, say, any automatic computer procedure (cf Garnatz & Hunt, 1973). Actually, an experienced investigator often possesses a 'feel' for data that is impossible to programme (e.g., he can readily recognize a single datum point that is severely in error). Another advantage with this manual approach is its flexibility: data often allow for more than one reasonable interpretation leading to different values of $L^p$, all of them being equally compatible with data. The scatter in the $L^p$ values gives some idea of the uncertainty involved. In this study we have found that the scatter is reasonable and we have as a rule selected the largest $L^p$ value. The reason for this policy is that because the kinetics is cut off at the $t_n$=24 h, almost any numerical procedure is bound to miss the 'tail' and thereby underestimate $L^p$.

The computer programme, utilizing the method of curve peeling, generated a family of approximately 500 functions of the form of Eq. 4. One curve from this family was selected on the basis of minimizing the sum of the absolute magnitudes of the errors between the generated function and the interpretation curve. (Incidentally, almost invariably the same generated curve also minimized the error with respect to the raw data.) The programme was constructed such that given the interpretation curve it estimated and presented the following:

(1) The L value as a function of $\tau$ (the time interval between drug administration) 3, 4, 6, 8, 12, 24 hours

(2) An estimate of the number of days required before steady state is achieved, as a function of $\tau$

(3) An estimate of the fluctuation as a function of $\tau$ (see Figure 1).

We have investigated the theory's applicability in connection with lithium therapy; i.e. to predict $L(\tau)$ for individual patients using data derived from a single loading dose of lithium, with subsequent blood sampling during the following

24 hours. The data generated for the estimation of $L(\tau)$ will give us variation in dosage pattern; e.g. the fluctuations one can expect when giving the medication one to six times a day (this will show the regimen needed to keep the plasma level within the desired limits), and the time required before the patient reaches steady state on any particular regimen.

## Methods

Five ml clotted blood was separated within 2 h of collection. Serum lithium was determined by atomic absorption spectrophotometry with a Model 303 Perkin-Elmer instrument with a 3-slot Boling burner head. Serum was diluted 1 to 5 (0·5 ml/2·0 water) in distilled water and the standards matched in viscosity and other electrolyte concentrations by the addition of a comparable serum not containing lithium. The coefficient of variation of this method is $<1{\cdot}0\%$.

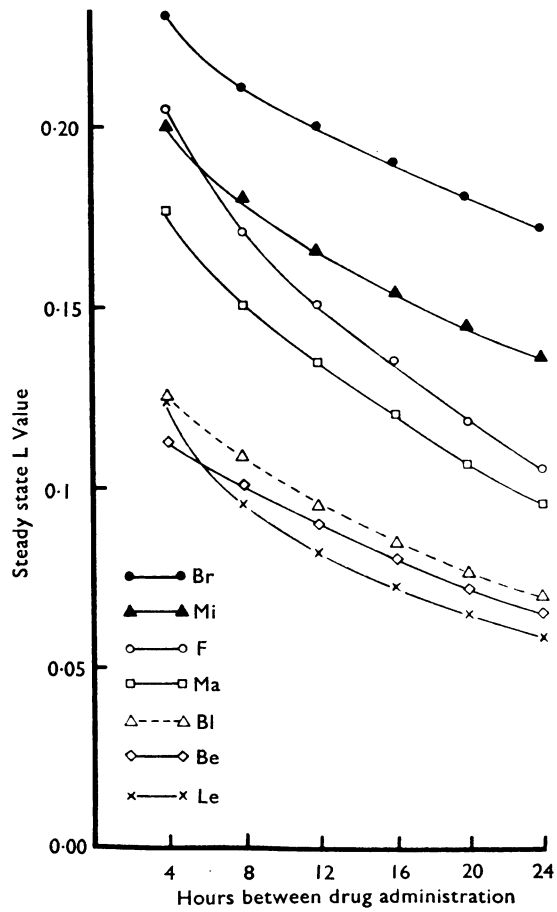


FIG. 2. The predicted L-values for seven different patients plotted as functions of $\tau$, i.e. the time distances between consecutive drug administrations. Note that the curves are 'normalized' in the sense that they all refer to the same 24 h dose: e.g. if $\tau=4$ it means that this unit dose is fractionated into six equal portions.

*Patient selection*

Patients were selected by one of us (GMS) as suitable subjects for this medication. Each subject was then given either 300 or 600 mg lithium in tablet form, and blood samples collected at 0·5, 1, 2, 3, 4, 6, 8 and 24 h after this administration. From these data were predicted the steady state level, the fluctuations in steady state level, and the time taken to achieve steady state for unit dose were calculated. The patients were then prescribed their medications by GMS who, at that point, had no idea of the kinetic predictions. Blood samples were taken and the medication increased until a satisfactory steady state level was achieved. Blood samples were always collected immediately prior to the patient taking the next tablet or tablets.

**Results**

Throughout this section all results refer to the patient receiving the same total dose per 24 hours.

Figure 2 shows the very large differences between seven subjects in the steady state L values (predicted from kinetic data). It will also be seen that the more frequently the drug is administered, the larger is the L value.

Figure 3 indicates the large difference in time required to reach steady state. Thus subject Br has a range of 4 to 7 days depending upon the frequency of drug administration, whereas for subject Le little is achieved by dividing the dose.

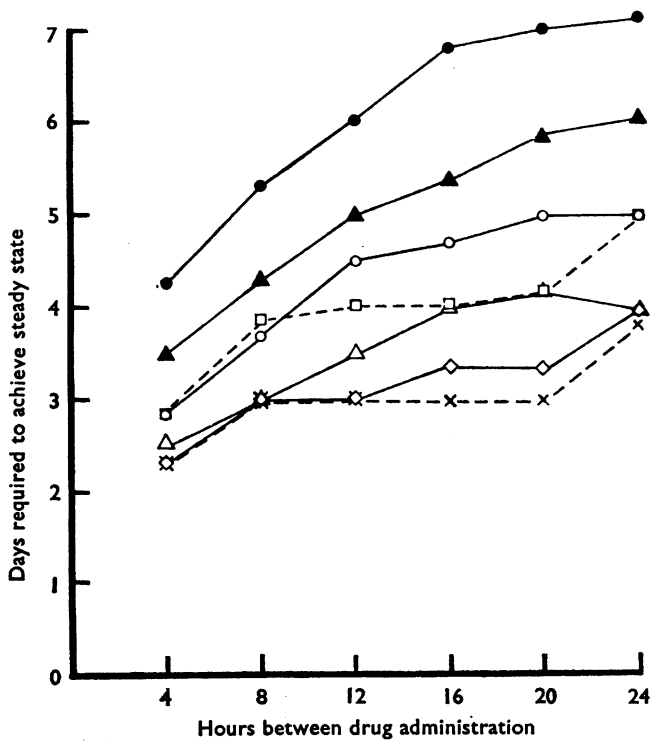


FIG. 3. Days required to achieve steady state plotted as functions of $\tau$ (see the text of Figure 2). The identification symbols are the same as those for Figure 2.

However, as can be seen from Fig. 4 (subject Br), the less often the medication is given the larger the fluctuations between the L and H values. If the interval between medication is 24 h, there is, in this case a fluctuation of approximately 100% of the L value.

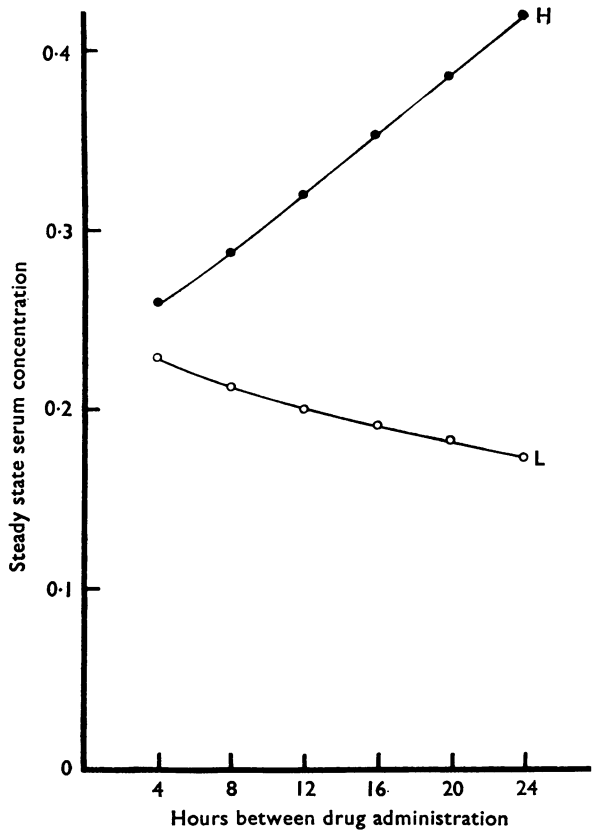


FIG. 4. The L and H values for subject Br (see Fig. 2) plotted as functions of $\tau$. Note that when the daily dose is administered only once a day (i.e. $\tau=24$), the difference between H and L is approximately 100% of the L value.

TABLE 1.

| Patient | Daily regimen | Predicted L value mEq/litre | Actual L value range mEq/litre |
|---|---|---|---|
| L.E. | 300 mg×3 | 0·29 | 0·42–0·61 |
| M.I. | 300 mg×3 | 0·54 | 0·58–0·81 |
| M.A. | 300 mg×4 | 0·60 | 0·27–0·77 |
| P.B. | 300 mg×2 | 0·18 | 0·18–0·33 |
| | 300 mg×1 | 0·07 | 0·06–0·09 |
| R.B. | 600 mg×4 | 1·0 | 1·09–1·40 |
| F.R. | 300 mg×4 | 0·82 | 0·52–0·82 |
| B.R. | 300 mg×3 | 0·63 | 0·45–0·58 |
| | 300 mg×4 | 0·88 | 0·73–0·98 |
| K.Z. | 300 mg×2 | 0·33 | 0·30–0·46 |
| H.B. | 600 mg×3 | 0·86 | 0·75–1·42 |
| D.W. | 600 mg×3 | 0·62 | 0·69–0·92 |
| T.D. | 300 mg×3 | 0·46 | 0·37–0·59 |
| S.P. | 300 mg×4 | 1·02 | 0·76–1·23 |
| V.R. | 300 mg×3 | 0·81 | 0·87–1·04 |
| A.P. | 300 mg×4 | 1·2 | 1·08–1·23 |
| A.H. | 300 mg×2 | 0·80 | 0·65–0·81 |

Table 1 shows that the observed values are in reasonable agreement (clinically acceptable) with the predicted. At this time we have been unable to explain the discrepancy shown by patient Le. It is also obvious that the individual subjects exhibit significant steady-state variation: the values given in Table 1 are the lowest and the highest L-values observed over a time period (in some cases over a month), when, theoretically, steady state had been achieved.

**Discussion**

The enormous spread in rates of biotransformation of psychopharmacological agents has been well documented by Sjoqvist, Hammer, Borga & Azarnoff (1969). Brodie (1964) has pointed out that one does not need statistics to deduce that the biological effects of a drug are much more closely related to the plasma or tissue level than to the dose.

The experiments described above are an attempt at a feasible method of predicting each individual patient's dosage requirements. An additional advantage has been the possibility of examining the fluctuations in the steady state level on different dose regimens. Further studies indicate that this method should be a valuable tool in the determination of drug interactions. Thus, if medication A is given in a single dose and the plasma concentration curve observed over a suitable time period, medication B can then be given over some period of time (e.g. two weeks), after which another single dose of A is given and, again, the plasma concentration curve is recorded. Analysis of the two curves should indicate whether any change in the A-metabolism has taken place, and consequently, whether there is any metabolic drug interaction, i.e. whether B changes A.

As research tool the present approach may also prove useful for detection of ' short-term ' systemic adaptation, e.g. the presence of almost immediately induced catabolic enzymes. Thus, as pointed out earlier, the numerical procedure that we have applied is likely to lead to under-estimates of the L-values (cf. Table 1), and, therefore, if the predicted L-values should be consistently above the actually observed ones it would be a strong indication that such an enzyme system exists. Slowly induced enzymes can, of course, be detected by more conservative non-kinetic methods.

It is our goal to apply this method of analysis of curves from other psychopharmacological drugs. Techniques are available in which isotope derivative formation and/or chromatographic separation are used for the estimation of the plasma levels of these drugs and their metabolites. The application of the technique to drug interaction studies is an interesting prospect.

Drugs used in psychopharmacology are highly lipid soluble compounds and the unchanged agents are virtually non-existent in urine or faeces and, therefore, the metabolism of the drug is the major pathway to elimination. Hence, if the theory applied to the present data proves applicable to other drugs we will have a tool close to the ideal described by Cash & Quinn (1970) namely, ' the ability to assess a patient's drug inactivating capacity '.

Finally, there are some points in our choice of numerical procedure and measure of goodness of fit that require amplification. A common measure of fit is the sum of squared deviations, but it is also well known that of two models (mathematical functions) the one that gives the best fit to data in this sense is not necessarily the

best prediction. Hence, when we found a function (Eq. 4) that on the whole gave clinically useful predictions, we could not see any reason to extend the study further to problems of numerical and statistical analysis. We are convinced that the occasional discrepancies between predicted and observed L values are not due to the numerical methods but a result of working with clinical data.

The choice of curve peeling instead of the currently popular iterative parameter estimation is because we have found empirically that the latter part of the curve is of prime importance in predicting L values: with the curve peeling technique the parameters that mainly represent that part of the curve are less influenced by the statistical errors in the remaining estimators.

The purpose of this investigation has been to see whether kinetic data do contain clinically significant information and to see how patients differ with respect to their response to changes in dose regimen, and not to statistically evaluate various numerical procedures.

This work was supported in part by Grant Nos. MH 17566, MH 07292 and FR 05651 from the National Institute of Mental Health, Bethesda, Md. U.S.A.

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(*Received October* 25, 1972)