Relationship Between Elimination Rate of Drugs and Rate of Decline of Their Pharmacologic Effects

Sir:

Recent advances in the mathematical analysis of the kinetics of drug absorption, metabolism, and excretion make it timely to consider the relationship between the time course, after drug administration, of drug content in the body and the time-intensity course of the pharmacologic effect elicited by the drug. Of particular interest is the nature of the relationship between drug elimination rate and the rate of decline of a pharmacologic effect. It has been pointed out previously (1) that several factors can account for appreciable differences in rates of these two processes; the rate of decline of a pharmacologic effect may be related, among other factors, to the rate of reformation of an essential enzyme, to the rate of drug diffusion from a target site, to the rate of elimination of a pharmacologically active metabolite, or it may even be characteristic of the effect itself rather than of the drug (2). The rate of decline of certain types of pharmacologic activity can be modified also by physiologic compensatory (homeostatic) mechanisms. It is proposed to examine here the relatively uncomplicated case in which the administered drug is pharmacologically active as such, its biotransformation products are inactive, and the intensity of pharmacologic activity at any given time is some function of the amount of drug in the body at that time. It is assumed, for the sake of simplicity, that drug absorption is instantaneous (as would be the case upon intravenous administration).

It is found frequently that the intensity of a pharmacologic effect is related linearly, over a considerable range, to the logarithm of the administered amount of drug (3). Thus

$$E = m \log A + e \qquad \text{(Eq. 1)}$$

where E is the intensity of the pharmacologic effect, A is the amount of administered drug, m is the slope of the line when E is plotted *versus* log A, and e (which usually is a negative quantity) is the intercept of the line on the E axis. Equation 1 may be expressed

$$\log A = \frac{E - e}{m} \qquad \text{(Eq. 2)}$$

Considering the common case where drug elimination follows first-order kinetics

$$\log A = \log A_0 - \frac{K}{2.3} t \qquad \text{(Eq. 3)}$$

where A is the amount of drug in the body at time t, A_0 is the intercept at zero time of the extrapolated linear portion of a plot of the logarithm of A *versus* time, and K is the first-order elimination rate constant for the drug. Substituting for log A and log A_0 in Eq. 3 from Eq. 2 yields

$$\frac{E - e}{m} = \frac{E_0 - e}{m} - \frac{K}{2.3} t \qquad \text{(Eq. 4)}$$

which, upon multiplication of each term by m and rearrangement, results in

$$E = E_0 - \frac{Km}{2.3} t \qquad \text{(Eq. 5)}$$

Also

$$E = E_0 - \frac{0.3m}{t_{1/2}} t \qquad \text{(Eq. 6)}$$

where $t_{1/2}$ is the biologic half-life of the drug. Significantly, Eqs. 5 and 6 are zero order and, under these conditions, the rate of decline of pharmacologic activity is a function of drug elimination rate and of m, with the latter value reflecting quantitatively (over the applicable range) the proportionality between intensity of the pharmacologic effect and the logarithm of the amount of drug in the body.

It is not uncommon to find apparent zero-order

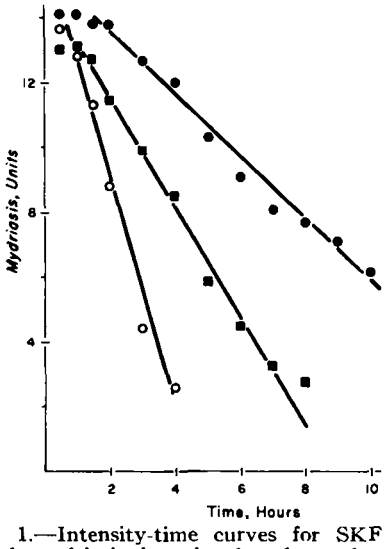

Fig. 1.—Intensity-time curves for SKF 5516-induced mydriasis in mice based on data from Sturtevant (5). Differences in slopes suggest variation of K with dose (see text). Key: ●, 3 mg./Kg.; ■, 1 mg./Kg.; ○, 0.3 mg./Kg., intravenously.

rates of decline of pharmacologic activity described in the pharmacologic literature. For example, the time course of mydriatic response by mice to atropine is apparently zero order; this is particularly interesting in view of the excellent linearity of the response *versus* log dose plot obtained in the same study (4). The time course of mydriatic response to two other anticholinergic drugs has been described recently in terms of first-order kinetics (5), yet the data are, in fact, much more representative of zero-order kinetics (for example, see Fig. 1). Naturally, the occurrence of apparent zero-order kinetics in the decline of pharmacologic activity, while consistent with the kinetic relationship developed here, cannot prove its existence. Moreover, none of these comments should be interpreted as ruling out the theoretical basis for the occurrence of first- or second-order kinetics with respect to the rate of decline of some types of pharmacologic activity.

Perhaps the most important conclusion to be derived from the present discussion is this: the frequent reasoning (see, for instance, the references cited by Schaumann and Stoepel (6)) that the pharmacologic effect is likely to decline exponentially because the body drug content does is intrinsically wrong unless the intensity of a pharmacologic effect is a linear function of the dose. The latter occurs quite infrequently, although we have recently reported one such case (7). It seems desirable, therefore, to be circumspect in depicting activity *versus* time data and to consider the possibility of a linear decline of activity with time.

The relationship expressed in Eq. 5 has interesting implications. It indicates that, despite a direct relation between body drug content and intensity of the elicited pharmacologic effect, rates of decline of these two quantities can follow different kinetics and, therefore, not be parallel. Since not only K but also m can vary significantly in a series of similar pharmacologic agents (8), the possibility presents itself, through the design and choice of agents with different K/m ratios, of modifying the relationship between the time course of body drug content and the time-intensity course of a pharmacologic effect. This may be a means of reducing certain side effects associated with a given class of chemotherapeutic agents. The K/m ratio may also be a useful additional parameter for characterizing the properties of certain drugs.

(1) Levy, G., in "Prescription Pharmacy," J. B. Lippincott Co., Philadelphia, Pa., 1963, Chapter 2.
(2) Levy, G., "Proc. Annual Research & Scient. Development Conference," Proprietary Association, Washington, D. C., 1961, p. 32.
(3) Randolph L. K., and Cimminera, J. L., in "Remington's Practice of Pharmacy," 12th ed., Mack Publishing Co., Easton, Pa., 1961, Chapter 9.
(4) Quinton, R. M., *J. Pharm. Pharmacol.*, 15, 239(1963).
(5) Sturtevant, F. M., *Proc. Soc. Exptl. Biol. Med.*, 104, 120(1960).
(6) Schaumann, W., and Stoepel, K., *Arch. Exptl. Pathol. Pharmakol.*, 245, 518(1963).
(7) Levy, G., Calesnick, B., and Wase, A., *J. Nucl. Med.*, in press.
(8) Wiberg, G. S., and Stephenson, N. R., *J. Pharm. Pharmacol.*, 13, 416(1961).

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Tumor Inhibitors III. Monocrotaline, the Active Principle of *Crotalaria spectabilis*

Sir:

In the course of a continuing screening program for tumor inhibitors from plant sources, an alcoholic extract of the fruits of *Crotalaria spectabilis* Roth,[1] was found to have reproducible activity against adenocarcinoma 755 in mice.[2] We report herein the fractionation of the active extract and the isolation and characterization of the active principle, monocrotaline.

Preliminary studies of the alcoholic extract indicated that partition between chloroform and water resulted in concentration of the activity in the water phase. Upon treatment of the aqueous solution with dilute aqueous alkali, the active principle was liberated from its salt form and became extractable into chloroform. The systematic procedure which was subsequently developed for isolation of the active alkaloid started with extraction of dried ground plant material in a Soxhlet extractor with 95% ethanol. After concentration of the extract under water pump pressure, a thick brown resinous solid was obtained. Partition between

[1] Gathered in North Carolina, November, 1962. The authors acknowledge with thanks the receipt of the dried plant material from Dr. Robert E. Perdue, Jr., U. S. Dept. of Agriculture, Beltsville, Md., in accordance with the program developed with the U.S.D.A. by the Cancer Chemotherapy National Service Center.

[2] Assays were performed by the Wisconsin Alumni Research Foundation under contract to the Cancer Chemotherapy National Service Center. The procedures were those described in *Cancer Chemotherapy Rept.*, 25, 1(1962).