Kinetics of Pharmacologic Activity of Succinylcholine in Man

Sir:

Studies of the kinetics of pharmacologic effects of drugs in man are only in their beginning. The limited knowledge of this aspect of pharmacokinetics restricts considerably the utility of mathematical analyses of the kinetics of drug absorption, distribution, and elimination. This author has recently developed a number of mathematical expressions which relate the time course of pharmacologic activity of a drug to its apparent first-order rate constant for elimination, to the nature of its dose-response relationship, and to the dose given (1–5). While they have been found to describe satisfactorily the time course of pharmacologic activity of a number of drugs (5), a relatively rigorous evaluation of these mathematical expressions has been difficult due to the paucity of quantitative clinical data. A very extensive quantitative clinical study of the effects of the skeletal muscle relaxant succinylcholine in man by Walts and Dillon (6) has now provided an opportunity for a thorough evaluation of the pharmacokinetic formulations developed in previous reports from this laboratory (1–5).

Walts and Dillon (6) administered succinylcholine chloride in doses of 0.5, 1.0, 2.0, and 4.0 mg./Kg. body weight to a total of 120 patients under general anesthesia and determined the effect of this drug on the contraction of a skeletal muscle (thumb adduction) in response to stimulation of its motor nerve (ulnar nerve at the wrist). The results of their study form the basis of the pharmacokinetic analyses which follow.

It has been proposed that the duration (t) of a pharmacologic effect elicited by a drug given intravenously may be related to its dose (A_0) by the expression:

$$t = \frac{2.3}{k} \log A_0 - \frac{2.3}{k} \log A_{\min.} \qquad \text{(Eq. 1)}$$

where k is the apparent first-order rate constant for elimination, and $A_{\min.}$ is the minimum effective dose. The derivation of the equation and the assumptions upon which it is based have been outlined previously, and the linear relationship between duration of effect and logarithm of dose predicted by the equation has been shown to occur with several drugs (5). It has been pointed out that the equation should hold for any arbitrary end point (for example, 20, 80, or 100% of a normal value for grip strength) (5). A rigorous test of the applicability of Eq. 1 would be to demonstrate that the slope of the line obtained by plotting t *versus* log A_0 is the same regardless of the end point used. Such a test is now possible with the data of Walts and Dillon (6). Figure 1 shows that (*a*) there is a linear relationship between the duration of a given degree of muscular paralysis and the logarithm of the dose of succinylcholine, and (*b*) the slopes of the respective lines for 3 different end points are essentially the same. The apparent first-order elimination rate constant for succinylcholine determined from these slopes is 0.20 reciprocal minutes. $A_{\min.}$ values for 10, 50, and 90% muscle paralysis were calculated by use of Eq. 1; a plot of the logarithm of these values against the intensity of the pharmacologic effect yields a straight line (inset of Fig. 1).

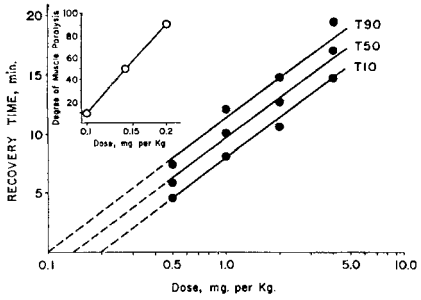

Fig. 1—Relationship between intravenous dose of succinylcholine chloride and duration of various degrees of neuromuscular inhibition in human subjects. T10, T50, *and* T90 *are the times required to recover 10, 50, and 90% of normal muscle contraction force. The data are from* Reference 6 *and represent average values from 13–16 subjects for each dose. Inset: intensity of effect* vs. *log dose, based on dose values obtained by extrapolation of duration of effect* vs. *log dose plots.*

The rate of decline of a pharmacologic effect with time should be constant (rather than exponential) if (*a*) the drug is eliminated by apparent first-order kinetics, (*b*) there is a linear relationship between the logarithm of the dose and the intensity of the elicited pharmacologic effect, and (*c*) certain other requirements are met (5). Specifically,

$$E = E_0 - \frac{km}{2.3} t \qquad \text{(Eq. 2)}$$

where E is the intensity of the pharmacologic effect at time, t, k is the apparent first-order rate constant for drug elimination, m is the slope of the linear portion of a plot of E *versus* log dose, and E_0 is the intercept at zero time of the extrapolated linear portion of a plot of E against t (5). Since the requirements listed above are met by succinylcholine, the intensity of its effect should

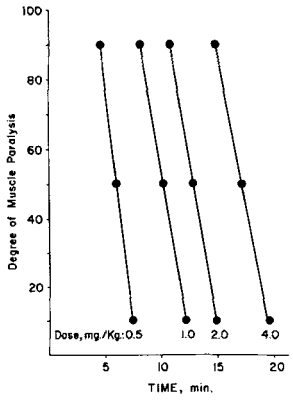

Fig. 2—Degree of muscle paralysis as a function of time after intravenous administration of 0.5 to 4.0 mg./Kg. succinylcholine chloride to groups of 13–15 human subjects. Data from Reference 6.

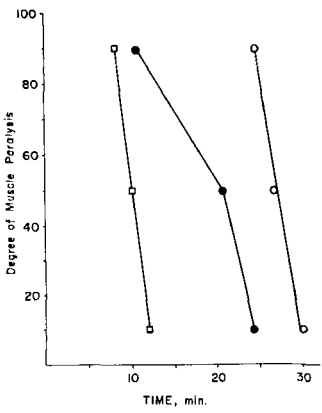

Fig. 3—Degree of muscle paralysis as a function of time after intravenous and intramuscular administration of succinylcholine chloride to human subjects. Key: □, 1 mg./Kg. i.v., 15 subjects; ●, 1 mg./Kg. i.m., 7 subjects; ○, 2 mg./Kg. i.m., 9 subjects. Data from Reference 6.

decline linearly with time, the rate of decline being independent of dose. This is indeed the case with doses ranging from 0.5 to 4 mg./Kg. (Fig. 2). The apparent first-order rate constant for elimination of succinylcholine, as determined from the slopes in Fig. 2 (which yield values of *km*) and the response-log dose plot shown as the inset in Fig. 1 (which yields the value of *m*) is 0.18 reciprocal minutes. This value, obtained from *terminal* pharmacologic activity data (*i.e.*, from the last 0.2 mg./Kg. of each dose), is in very good agreement with the 0.20 $min.^{-1}$ value obtained from *total* pharmacologic activity data (*i.e.*, duration of effect from doses up to 4 mg./Kg.).[1] These results demonstrate therefore the successful application of both equations to the data and provide further support for the contention that the kinetics of many pharmacologic effects of drugs in man can be described adequately by means of appropriate mathematical expressions.

An interesting example of the use of pharmacologic activity data for biopharmaceutic analyses is provided by the data shown in Fig. 3. It is evident that the intensity of pharmacologic activity after intramuscular administration of 1 mg./Kg. succinylcholine declines more slowly than after the same dose given intravenously. This shows that the drug is still being absorbed from its intramuscular injection site. The activity decline slope following the 1 mg./Kg. intramuscular (i.m.) dose approaches that obtained with the i.v. dose when 10–15% of the i.m. dose remains in the body (as evident by reference to the log dose-response plot in Fig. 1). In the case of the 2 mg./Kg. i.m. dose, the activity decline 25 min. after injection is similar to that following an i.v. dose, showing that absorption is essentially complete when about 10% of the i.m. dose remains in the body. This consistency in the data from the 1 mg./Kg. and 2 mg./Kg. doses suggests, as a first approximation, that absorption was by first-order kinetics. Additional information for doses between 1 mg./Kg. and 2 mg./Kg. would permit more definitive conclusions. Thus, a kinetic analysis of pharmacologic activity data is useful not only in clinical pharmacology where it can be employed to establish the most effective dosage regimen for a drug, but also in biopharmaceutics where it can be applied for the evaluation of dosage form effects (5).

[1] This rate constant reflects the rate of decline of drug concentration at the neuromuscular junction; the rate-limiting step in this process is probably diffusion of succinylcholine from that site to the blood rather than enzymic hydrolysis in the blood (7).

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