Dose-Dependent Decline of Pharmacologic Effects of Drugs with Linear Pharmacokinetic Characteristics

MILO GIBALDI and GERHARD LEVY▲

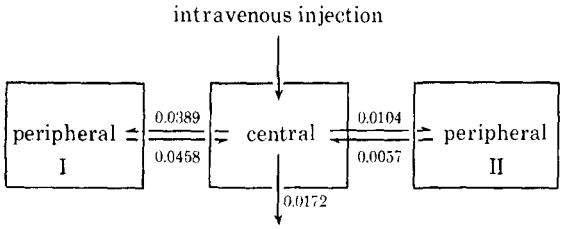
Abstract □ It is shown that reversibly acting drugs that confer on the body the pharmacokinetic characteristics of a multicompartment system may elicit pharmacologic effects which decline in the clinically significant range at an apparently constant rate which decreases with increasing dose. This dose dependence is illustrated by the neuromuscular blocking effect of tubocurarine in man.

Keyphrases □ Pharmacokinetics, multicompartment systems—dose-dependent decline of pharmacological effects, computer simulations □ Computer simulations—dose-dependent decline of pharmacological effects of drugs with linear pharmacokinetic characteristics □ Dose-dependent decline of pharmacological effects—multicompartment systems, computer simulations

It has been shown that pharmacologic effects of reversibly acting drugs are likely to decline at an approximately constant rate independent of dose in the clinically significant effect range (about 20–80% of the maximum effect)[1] if drug elimination from the body is a monoexponential process, the relationship between the intensity of the effect and the *logarithm* of dose is approximately linear in the clinically significant range, and drug metabolites are essentially inactive pharmacologically (1, 2). Specifically:

$$\text{rate} = km/2.3 \qquad \text{(Eq. 1)}$$

where rate is the rate of decline of the pharmacologic effect, k is the apparent first-order drug elimination rate constant, and m is the slope of the intensity of effect–log dose relationship. Equation 1 alone or in combination with the duration of effect *versus* log dose equation (3) has been useful in the pharmacokinetic analysis of various pharmacologic effect data (1, 2, 4, 5). Recently, detailed studies of multicompartment pharmacokinetic systems have revealed a number of significant differences in kinetics of pharmacologic effects relative to single-compartment systems (6). As an extension of these studies, the time course of the decline of pharmacologic effects of multicompartment-type drugs has been investigated as a function of dose. The computer simulations presented here are based on pharmacokinetic constants derived in a previously reported study of the kinetics of tubocurarine elimination and neuromuscular blocking effect in man (7). This drug has distinct multicompartment characteristics, and experimental data describing the decline of its effect in man as a function of dose are available (8, 9) for comparison with theoretical predictions.



Scheme I—Pharmacokinetic model for tubocurarine distribution and elimination in man. Rate constants, in reciprocal minutes, are shown next to the arrows representing apparent first-order processes for transfer of drug between compartments and elimination from the central compartment. (From Reference 7.)

[1] The intensity of effect elicited by some drugs in the therapeutic dose range may be only a small fraction of the maximum attainable effect. This discussion does not apply to such drugs.

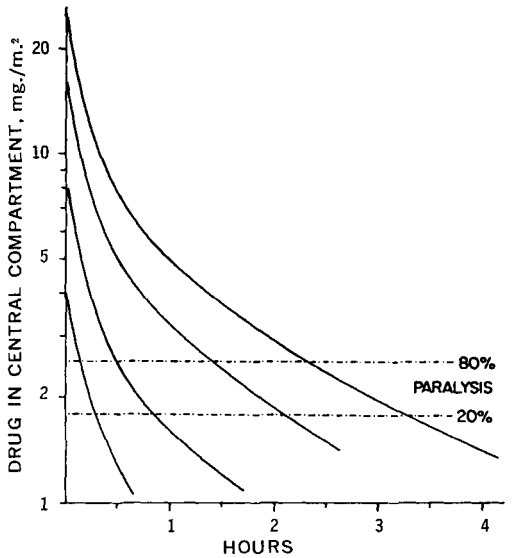


Figure 1—*Time course of tubocurarine (mg./m.² body surface area) in the apparent central compartment of human adults as a function of time and dose. The two horizontal lines represent the amount of drug in the central compartment required to elicit 80 and 20% paralysis of the adductor muscles of the thumb. (Based on pharmacokinetic data from* Reference 7.)

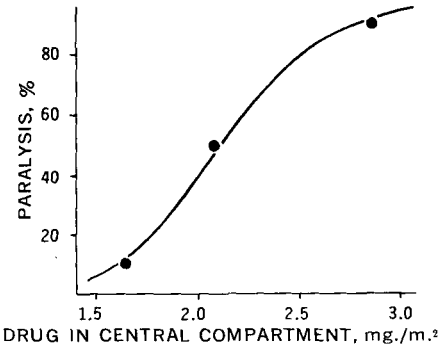


Figure 2—*Relationship between neuromuscular blocking effect of tubocurarine and amount of drug in central compartment of the body, with the experimental points fitted according to classical receptor theory (see text).*

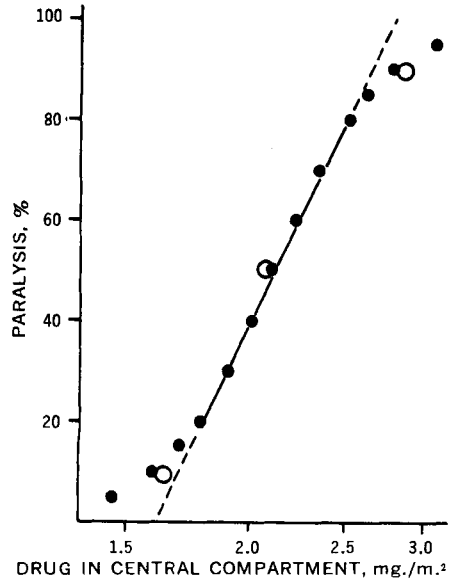


Figure 3—*Approximately linear relationship between neuromuscular blocking effect of tubocurarine and the logarithm of the amount of drug in the central compartment of the body in the 20–80% effect range. Key: ●, sigmoid curve shown in Fig. 2; and* ○, *experimentally derived data.*

METHODS

As shown previously (7), the kinetics of tubocurarine distribution and elimination may be characterized by a three-compartment linear model, with elimination from the central compartment (Scheme I). The site of the neuromuscular blocking effect is in the central compartment, and the amounts of drug required in that compartment to elicit different degrees of paralysis were calculated (7). The computer simulations presented here were carried out by means of the MIMED program (10) with a CDC 6400 digital computer. Experimental data are from Walts and Dillon (8) and Walts *et al.* (9), who determined the neuromuscular blocking effect of various intravenous doses of tubocurarine in subjects undergoing general anesthesia for surgical operations. The response of the adductor muscles of the thumb to supramaximal ulnar nerve stimulation was used as a measure of neuromuscular blockade.

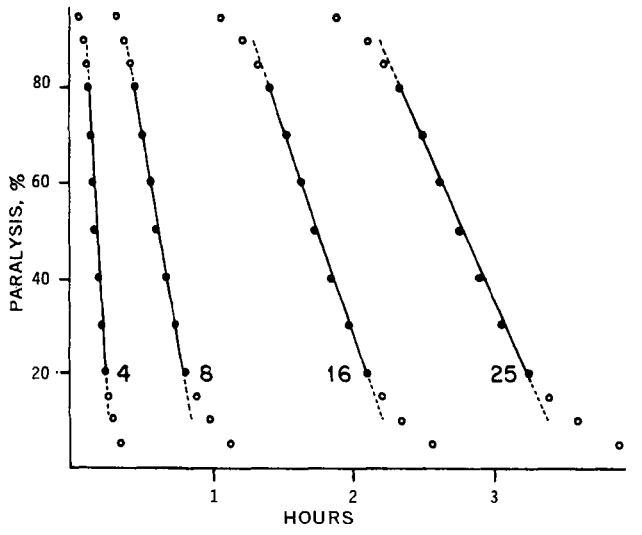


Figure 4—*Decline of neuromuscular blocking effect of tubocurarine as a function of time at various doses (mg./m.², indicated by number next to each curve). The open and closed circles represent calculated values based on the curves in Figs. 1 and 2; the closed circles represent values in the 20–80% effect range, fitted to straight lines.*

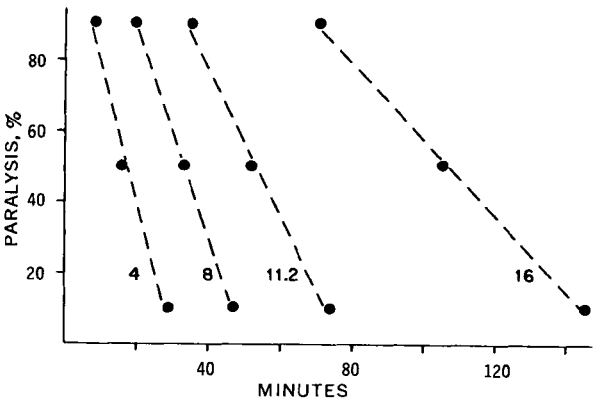


Figure 5—*Data reported by Walts and Dillon (8) showing the dose dependence of the rate of decline of the neuromuscular blocking effect of tubocurarine in man. Median values from 20 or 40 subjects. The stippled lines are to facilitate comparison of the different sets of data and have no theoretical basis. The numbers represent the size of the respective dose (mg./m.²).*

RESULTS AND DISCUSSION

Figure 1 depicts the time course of tubocurarine amounts in the central compartment of the body as a function of intravenous dose (4, 8, 16, and 25 mg./m.²). Shown also are the amounts of drug in the central compartment required to elicit 20 and 80% paralysis of the adductor muscles of the thumb. These amounts were determined from the "dose"–response curve in Fig. 2. The data points in that figure were calculated directly from experimental measurements (7); the curve is based on classical receptor theory (11), which yields the equation:

$$\ln \frac{R}{R_M - R} = s \ln c + \ln Q \qquad \text{(Eq. 2)}$$

where R is the intensity of the pharmacologic effect (as percent of the maximum effect R_M) corresponding to drug concentration c, s is the slope of a plot of $\ln [R/(R_M - R)]$ *versus* $\ln c$, and Q is the value of $[R/(R_M - R)]$ when $c = 1$ (12). The constants s and Q were evaluated from a plot of $\ln [R/(R_M - R)]$ *versus* ln amount of drug in the central compartment (dose). As shown in Fig. 3, points that fall directly on the classical dose–response curve of Fig. 2 can be fitted to a straight line in the 20–80% effect region when doses are plotted on a logarithmic scale. The slope of that line is 390%; the utility of this value will be pointed out subsequently.

By knowing the time course of the amount of tubocurarine in the central compartment (Fig. 1) and the relationship between intensity of effect and amount of drug in the central compartment (Fig. 2), it is possible to determine the decline of the neuromuscular blocking

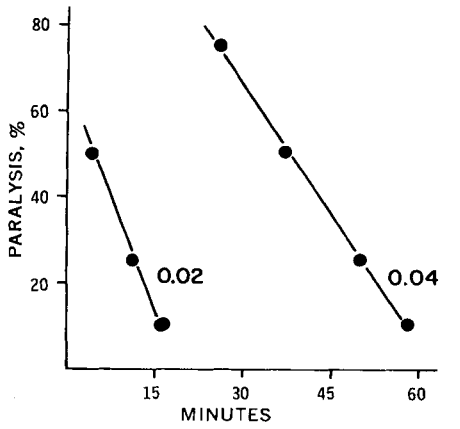


Figure 6—*Rate of decline of the neuromuscular blocking effect of pancuronium in man as a function of dose (mg./kg., indicated by number next to each curve). Average of 16 and 10 adult subjects for the low and high dose, respectively. (Data from* Reference 13.)

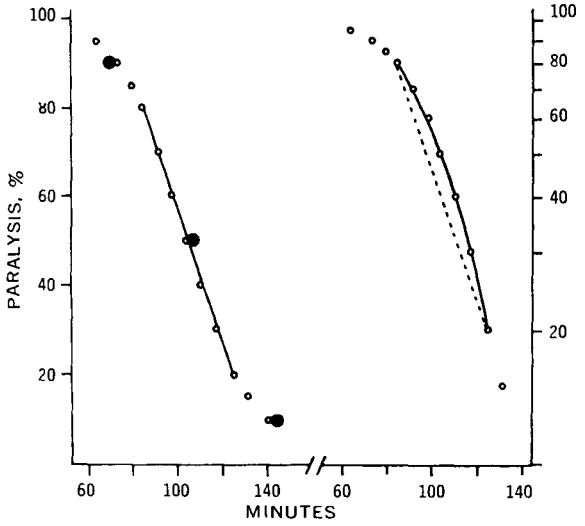


Figure 7—*Decline of the neuromuscular blocking effect of 16 mg./m.² tubocurarine as a function of time, plotted on a linear (left) and logarithmic (right) ordinate scale. The linear plot is straight in the 20–80% range and the semilogarithmic plot is curved in the same range. Key: ○, calculated values from the curves in Figs. 1 and 2; and ●, experimental data from Walts and Dillon (8).*

effect of tubocurarine with time at various doses. The results show that the effect declines at an essentially constant rate in the 20–80% effect range, but the rate of decline decreases with increasing dose (Fig. 4). This dose dependence derives from the changing slope of the log amount of drug in the central compartment *versus* time relationship in any particular amount range as a function of dose (Scheme I). Drugs with single-compartment characteristics do not show this dose dependence in the rate of decline of pharmacologic effects, since the decline of amounts of drug in the body with time in a given amount range is independent of dose.

Direct experimental evidence for the dose dependence of the rate of decline of the neuromuscular blocking effect of tubocurarine in man is available in data reported by Walts and Dillon (8) and shown in Fig. 5. More recently, Walts *et al.* (9) determined the effect of a 32-mg./m.² dose in 10 patients and found 90% paralysis at 135 ± 39 min. and 10% paralysis at 267 ± 62 min. These times are in good agreement with those determined by theoretical calculations based on the pharmacokinetic model discussed here (156 and 261 min., respectively) and represent an even slower decline of effect than that of the 16-mg./m.² dose in Fig. 5.

Another neuromuscular blocking agent, pancuronium, which is also a multicompartment-type drug as judged by its dose–duration of effect relationship (6), similarly exhibits dose dependence in the rate of decline of its effect in man (Fig. 6). The linear but dose-dependent decline of the mydriatic effect of intravenously administered SKF-5516 (14) is another likely example of the phenomenon described here.

There is a practical reason why it is often useful to plot the decline of pharmacologic effects *versus* time on linear coordinates and to characterize this decline in the 20–80% effect region by an apparent zero-order rate constant. With tubocurarine as an example, it is evident in Fig. 7 that the decline of its effect is represented quite well by a straight line on linear coordinates in the 20–80% effect region while a semilogarithmic plot definitely does not yield a straight line in that region. By using Eq. 1, which assumes a linear relationship between effect and the logarithm of the amount of drug (such as is depicted in Fig. 3), it is possible to determine a value for k at various doses of tubocurarine from the slope value m and the rate of decline of effect at various doses of the drug. This k is obviously an apparent k and simply approximates the decline of the amounts of drug in the central compartment during the time when the intensity of effect ranges from 20 to 80% of maximum. Agreement between k values estimated from the simulated effect data and determined directly from simulated amount data is very good (Table I). This approach will be useful for estimating the time course of elimination of drugs for which no chemical assays are available but which produce readily quantifiable pharmacologic effects. These concepts can also be applied to a pharmacokinetic analysis of several different simultaneously occurring effects produced by a single drug (1).

Table I—Utility of Linear Approximations of the Rate of Decline of a Pharmacologic Effect to Estimate Apparent Drug Elimination Rate Constants

Tubocurarine Dose, mg./m.²	Rate of Decline[a], %/min.	$k_{app.}$, min.⁻¹ From Rate of Decline[b]	$k_{app.}$, min.⁻¹ From Drug Levels[c]
4.0	7.50	0.044	0.044
5.6	4.80	0.028	0.029
8.0	2.73	0.016	0.016
11.2	1.76	0.010	0.010
16.0	1.43	0.0084	0.0084
25.0	1.11	0.0065	0.0063

[a] Neuromuscular paralysis of the adductor muscles of the thumb; rate of decline estimated in the 20–80% effect range. [b] Based on rate of decline of effect = $k_{app.}\ m/2.3$, where m = 390%. [c] Based on $k_{app.}$ = 2.3 (log $A_{80\%}$ − log $A_{20\%}$) $(t_{20\%} - t_{80\%})^{-1}$, where A and t are the amount of drug in the central compartment and the time, respectively, when the neuromuscular blocking effect is 80 or 20% of maximum.

In summary, it has been shown that intravenously administered multicompartment-type drugs with linear distribution and elimination kinetics that obey the principle of superposition nevertheless are likely to exhibit dose dependence in the rate of decline of their pharmacologic effects. While this has been demonstrated here with respect to a drug that acts in the central compartment of the body, the same possibility exists for drugs with sites of action in peripheral ("tissue") compartments other than the "deepest" compartment.

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