Anesthesiology
V 36, No 3, Mar 1972

Kinetics of the Elimination and Neuromuscular Blocking Effect of d-*Tubocurarine in Man*

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A pharmacokinetic model for the distribution and elimination of *d*-tubocurarine in man has been evolved from plasma concentration and urinary excretion data reported previously. This model represents the body as a three-compartment linear system, with the site of action of *d*-tubocurarine being located in the central compartment on the basis of available knowledge of pharmacologic effects. Relationships between dose and duration of action and between dose and durations of effects of successive fractional doses administered after a constant initial dose have been predicted by the mathematical model and are in excellent agreement with experimental results. Additional simulations have been carried out to explore the effects of other dosage regimens of clinical interest for which experimental data are not presently available. (Key words: Kinetics; *d*-Tubocurarine; Neuromuscular block.)

THE ELUCIDATION of the kinetics of drug action in man is of major importance in the development of rational drug therapy. Nowhere is this requirement more readily evident than in anesthesiology, since this discipline involves the use of drugs with profound, readily apparent effects. These drugs must be administered in doses that elicit reasonably predictable intensities and durations of action. Previous studies in this laboratory have shown that the kinetics of drug action in man can often be characterized effectively on the basis of classic pharmacokinetic theory.[1-3] Recently, it has been possible to relate many unusual temporal patterns of drug action to the multicompartment distributional characteristics of the drugs.[4]

d-Tubocurarine's elimination in man has pronounced multicompartmental characteristics.[5, 6] A review of the literature revealed sufficient data describing plasma concentrations, urinary excretion, and pharmacologic activity to permit attempting an integrated pharmacokinetic characterization of the time course of the neuromuscular blocking effect of *d*-tubocurarine in man under clinical conditions. This characterization and associated explorations of clinically relevant dosage regimens are the subject of this report.

Methods

Urinary excretion data from Kalow[5] and plasma concentration data from various sources,[6, 7] obtained after intravenous injection of *d*-tubocurarine, were used to determine the constants for a tri-exponential decay curve of the form

$$X_c = Pe^{-\pi t} + Ae^{-\alpha t} + Be^{-\beta t} \qquad (1)$$

where X_c is the amount of drug in the central compartment § of the three-compartment system at time t, and P, π, A, α, B, and β are constants. These constants and the appropriate equations[8] to calculate apparent first-order rate constants and compartmental drug levels of the three-compartment open model depicted in figure 1 were used as digital computer input, using the MIMED program[9] and a CDC 6400 digital computer. Successive dosings were simulated by introducing the appropriate "doses" into the central compartment at indicated times after the simulated administration of the first dose. Pharmacologic effect data were obtained from the reports of Walts and Dillon,[10, 11] who determined duration of action of intravenously administered *d*-tubocura-

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Received from the Department of Pharmaceutics, School of Pharmacy, State University of New York at Buffalo, Buffalo, New York 14214. Accepted for publication August 19, 1971. Supported in part by a grant from Burroughs, Wellcome Company.

§ The central compartment consists of blood plasma and other "instantaneously" accessible fluids and tissues.

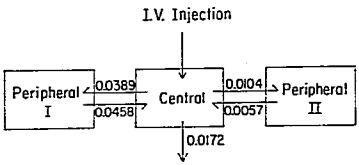

FIG. 1. Pharmacokinetic model for *d*-tubocurarine distribution and elimination in man. Rate constants, in reciprocal minutes, are shown next to the arrows, which represent apparent first-order processes for transfer of drug between compartments and elimination from the central compartment.

rine in subjects undergoing general anesthesia for surgical operations, using the response of the adductor muscles of the thumb to supramaximal stimulation of the ulnar nerve as a measure of neuromuscular blockade.

Results and Discussion

Plasma concentrations of intravenously administered *d*-tubocurarine in man decline in tri-exponential fashion. The available plasma concentration and urinary excretion data yielded the expression

$$\frac{X_e}{X_o} = 0.62e^{-0.1t} + 0.2Se^{-0.015t} + 0.10e^{-0.003t} \quad (2)$$

where X_e/X_o is the fraction of the dose in the central compartment at time t (in min), and all the numbers are constants. This equation, divided on both sides by the apparent volume of distribution of the central compartment, and multiplied by the dose, should describe the time courses of plasma concentrations of *d*-tubocurarine after intravenous injection. Considering the rate of renal excretion of *d*-tubocurarine to be proportional to the amount of the drug in the central compartment, equation 2 should describe the time course of urinary excretion of *d*-tubocurarine upon multiplying each side of the equation by the dose and by the excretion rate constant k_e. We obtained an excellent fit to the plasma concentration data of Cohen *et al.*,[7] as well as to the urinary excretion data of Kalow,[6] using an apparent volume of distribution of 72 ml/kg and a k_e value of 0.44 hours^{-1} (fig. 2). The latter was obtained by dividing the instantaneous excretion rate at a given time by the amount of drug in the central compartment at that time.

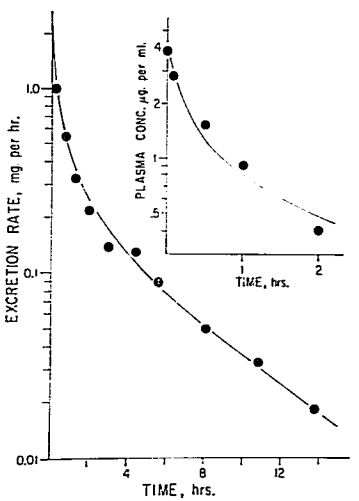

FIG. 2. Elimination kinetics of *d*-tubocurarine in man after intravenous injection. The curves are based on equation 2 of the text. The data points are urinary excretion rates of *d*-tubocurarine from Kalow[6] and (inset) plasma concentrations from Cohen *et al.*[7]

The tri-exponential elimination pattern of *d*-tubocurarine indicated the use of a three-compartment open model (fig. 1), assuming all processes to be linear and elimination to occur from the central compartment (which includes the plasma), which is connected to two peripheral, or tissue, compartments. The apparent first-order rate constants for this model, determined from the constants in equation 2, are shown in figure 1.

The site of the neuromuscular blocking action of *d*-tubocurarine could, in theory, be located in any one of the three hypothetical body compartments which make up the pharmacokinetic model. The neuromuscular sites could also constitute a distinct separate compartment pharmacokinetically. The very rapid onset of action of d-tubocurarine[12] suggests that its site of action is located in the central compartment. If this be so, the amount of drug in the central compartment at the time of recovery from the neuromuscular block should be independent of the dose adminis-

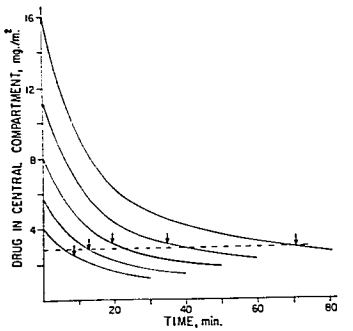

FIG. 3. Computer-simulated time courses of amounts of *d*-tubocurarine in the "central compartment" of the body after different intravenous doses. The arrows show the durations of the neuromuscular blocking effects (to 10 per cent recovery) of these doses, as reported by Walts and Dillon.[10] The broken line is the average of *d*-tubocurarine in the "central compartment" when the neuromuscular block is 90 per cent of maximum.

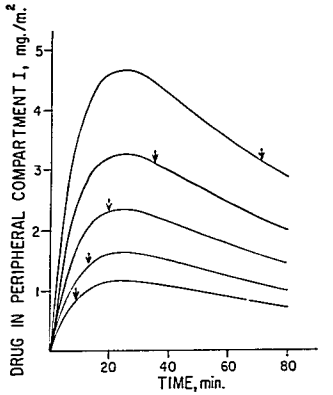

FIG. 4. Computer-predicted time courses of amounts of *d*-tubocurarine in the rapidly accessible "peripheral compartment I" of the body after different intravenous doses. The arrows have the same meaning as in figure 3.

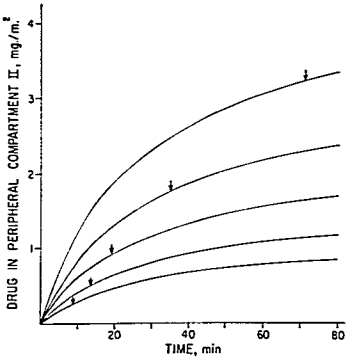

FIG. 5. Computer-predicted time courses of amounts of *d*-tubocurarine in the slowly accessible "peripheral compartment II" of the body after different intravenous doses. The arrows have the same meaning as in figure 3.

tered. Figure 3 shows the computer simulations of the amounts of *d*-tubocurarine in the central compartment of the body after intravenous injection of 4.0, 5.6, 8.0, 11.2, and 16.0 mg/m². The arrows indicate the durations of action to 10 per cent recovery of each of these doses as reported by Walts and Dillon.[10] As is evident, the amount of drug in the central compartment upon recovery from the effect of *d*-tubocurarine is indeed independent of dose. Similar results were obtained when 50 per cent recovery and 90 per cent recovery were used as the end points. In contrast, the amounts of drug in the rapidly and slowly accessible peripheral compartments at the time of recovery from neuromuscular blockade are definitely dose-dependent (figs. 4 and 5). Thus, the site of action of *d*-tubocurarine may be identified pharmacokinetically with the central compartment.

The amounts of *d*-tubocurarine in the central compartment after 10, 50, and 90 per cent recovery, respectively, from the neuromuscular blocking effects of 4.0, 5.6, 8.0, 11.2, and 16.0 mg/m² of the drug are listed in table 1. The average values yield a typical, essentially linear, effect–log "dose" curve (fig. 6). Knowing the minimum effective "doses" (actually the amounts of drug in the central compartment) for a given degree of paralysis, it is possible to predict the durations of effects of different doses. The curve in figure 7 represents the predicted durations of effect to 10 per cent recovery of *d*-tubocurarine in the 2- to-20-mg/m² dose range. This curve is in ex-

TABLE 1. Amounts of *d*-Tubocurarine in the "Central Compartment" of the Body when Neuromuscular Activity is Blocked 10, 50, and 90 Per Cent

Dose (mg/m² b.s.a.)	Drug in "Central Compartment" (mg/m²)		
	90 Per Cent Block*	50 Per Cent Block	10 Per Cent Block
4.0	2.45	1.74	1.23
5.6	2.81	1.90	1.62
8.0	3.13	2.26	1.85
11.2	3.07	2.48	1.94
16.0	2.85	2.03	1.55
Mean	2.86	2.08	1.64
Coefficient of variation (per cent)	9.4	14.0	17.2

* Note that 90 per cent block (or paralysis) is the same as 10 per cent recovery.

cellent agreement with average-duration data reported by Walts and Dillon.[10] On the other hand, a duration–log dose curve based on the two-compartment model originally proposed by Kalow[5] on the basis of urinary excretion data does not fit the clinical observations (fig. 8). The "disproportionate" increases in durations of effects of larger doses of *d*-tubocurarine[10] can be explained entirely on the basis of a linear multicompartmental model. There is no need to invoke saturation of nonspecific tissue acceptors[10] to explain this phenomenon. Walts and Dillon reported *mean* duration of effect data for 10 per cent recovery only, but they provided *median* results for 10, 50, and 90 per cent recovery.[10] The theoretically predicted durations and the clinical data (fig. 9) are in very good agreement. The 10 per cent recovery data are most precise (they have the lowest coefficient of variation) and show the best fit to the theoretical curve. The greater scatter of the 50 and 90 per cent recovery data are consistent with their larger coefficients of variation (table 1). The slight deviation from the theoretical curve of the data points representing the smallest dose reflects the time needed for the injected drug to distribute in the plasma and to diffuse to the endplates. This is also reflected by the approximately 30-second lag between time of injection and onset of effect.[12] While it is possible to incorporate these phenomena in the pharmacokinetic model, they are negligible quantitatively and thus do not justify a more complex model. It should be emphasized that the excellent agreement between simulated and experimental data was obtained with averaged-duration data and that individual patients differ in their responses to the drug.

Walts and Dillon have pointed out that wide variations in patients' responses to any single dose of *d*-tubocurarine make individual predictions of duration of effect unreliable.[10] Realizing that use of multiple doses of the drug tends to compensate for this lack of predictability, they determined the durations of effects of second doses administered upon recovery from the effect of the initial dose.[11] They expressed their empirical findings as cumulation ratios, which they defined as the duration of effect of the second dose divided by the duration of effect of the first dose. The utility of the pharmacokinetic model developed in the present study is illustrated effectively by the excellent agreement between the experimental results obtained by Walts and Dillon[11] and the computer predictions (table 2). Recognizing that it is often necessary to administer three or more doses, we have determined durations of effects of eight successive

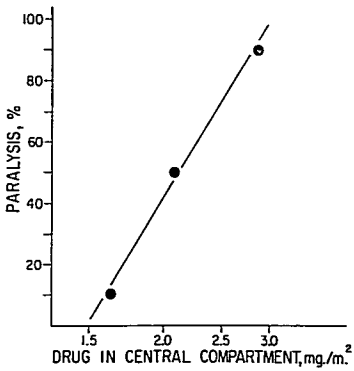

FIG. 6. Relationship between amount of *d*-tubocurarine in the "central compartment" of the body and magnitude of the neuromuscular blocking effect. Note that 90 per cent paralysis (or block) is the same as 10 per cent recovery.

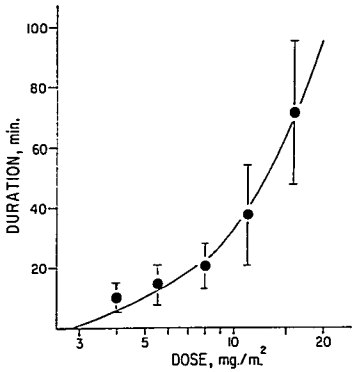

FIG. 7 (*above*). Relationship between dose of *d*-tubocurarine and average duration of neuromuscular blocking effect (to recovery of 10 per cent of normal twitch force) in man. The curve is the predicted relationship based on the kinetics of elimination of *d*-tubocurarine (fig. 2) and the calculated minimum effective "dose" (table 1). The data points (with standard deviations) are from reference 10 and represent average values from 20 or 40 subjects.

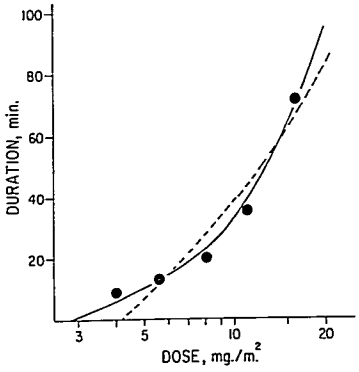

FIG. 8 (*top, right*). Comparison of theoretical predictions of the relationship between dose of *d*-tubocurarine and duration of its neuromuscular blocking effect. Continuous curve and data points as in figure 7; the broken curve was calculated on the basis of the two-compartment pharmacokinetic model originally presented by Kalow.[5]

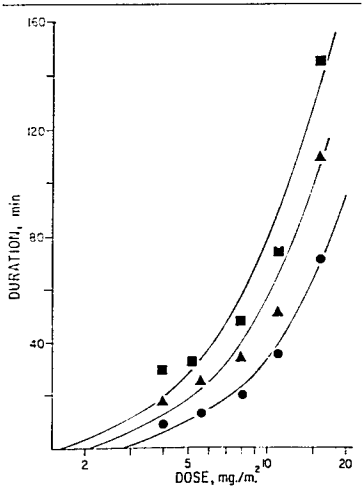

FIG. 9 (*right*). Relationship between dose of *d*-tubocurarine and median duration of action in man. The curves are the computer-predicted relationships. The data points are from reference 10 and represent the time necessary for recovery of 10 per cent (●), 50 per cent (▲), and 90 per cent (■) of the normal force of contraction of the adductor muscles of the thumb.

doses, with 8 mg/m² as the initial dose and 2, 4, and 8 mg/m², respectively, as the maintenance doses (table 3). According to these calculations, the duration of neuromuscular blocking effect increases with each successive dose. Although quantitative clinical data concerning the effects of several successive doses of *d*-tubocurarine apparently are not available, de Jong has stated recently that "when giving several doses of curare, its effect becomes increasingly greater."[13]

Finally, we have extended Walts' and Dillon's study of cumulation ratios by calculating these values for various doses of *d*-tubocurarine (table 4). These calculations show that the cumulation ratio is dose-dependent, decreasing with increasing dose. Thus, while the cumulation ratio is apparently a useful guide for determination of maintenance doses, it is not a constant, but is rather a dose-dependent value.

The present study illustrates and extends the concepts concerning the kinetics of pharmacologic effects developed in previous reports

TABLE 2. Predicted and Observed Durations of Effect of a Second Dose of *d*-Tubocurarine Administered after Recovery from an Initial Dose of 8 mg/m² b.s.a.

Second Dose (mg/m² b.s.a.)	Duration of Effect (Min)			
	Recovery to 10 Per Cent of Control		Recovery to 50 Per Cent of Control	
	Predicted	Observed*	Predicted	Observed*
2.0	18	18	—	—
4.0	32	36	51	41
8.0	61	69	90	90

* From reference 11.

TABLE 3. Predicted Durations of Effects of Successive Maintenance Doses of *d*-Tubocurarine Administered after an Initial Dose of 8 mg/m² b.s.a.

Dose	Duration of Effect (Min)*		
	Maintenance Dose 2 mg/m²	Maintenance Dose 4 mg/m²	Maintenance Dose 8 mg/m²
First (8 mg/m²)	23	23	23
Second	18	32	61
Third	21	41	77.5
Fourth	23	45	86
Fifth	24	48	92.5
Sixth	25.5	50.5	96.5
Seventh	26.5	52.5	99.5
Eighth	27	54.5	100.5

* End point: recovery to 10 per cent of control.

TABLE 4. Cumulation Ratio of Second Dose of *d*-Tubocurarine as a Function of Dose, Based on Computer Simulation

	Dose		
	4 mg/m²	8 mg/m²	12 mg/m²
Duration* of effect of first dose (I) (min)	5.5	23	45
Duration* of effect of second dose (II) (min)	20.5	61	98
Cumulation ratio, II:I	3.7	2.7	2.2

* End point: recovery to 10 per cent of control.

from this laboratory.[1-4, 14, 15] The pioneering work of Kalow[5] and the excellent clinical data of Walts and Dillon,[10, 11] which have also led to an effective pharmacokinetic characterization of the neuromuscular blocking effect of succinylcholine,[2] have been essential to the development of a useful pharmacokinetic model for *d*-tubocurarine. With adequate input data, it will now be possible to design suitable *individual* dosage regimens, to quantify the effects of physiologic variables such as body temperature and protein binding, and thereby eventually to develop the capability for rapid guidance by computer or nomogram in the selection of appropriate dosage regimens by the anesthesiologist.

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