Anesthesiology
50:528–533, 1979

Dosage-schedule Independence of d-*Tubocurarine Pharmacokinetics and Pharmacodynamics, and Recovery of Neuromuscular Function*

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To study the relationship of *d*-tubocurarine (*d*Tc) dosage schedule to its pharmacokinetics and pharmacodynamics, and recovery of neuromuscular function, 30 patients were given markedly different doses of *d*Tc to produce 90 per cent or greater depression of twitch tension for two hours during stable halothane anesthesia. Ten patients each were given *d*Tc in one of three dosage schedules: 20 mg/m² as a single large bolus; repeated smaller doses of 5 mg/m²; or a continuous infusion. After two hours of neuromuscular blockade, all patients experienced spontaneous recovery to 10 per cent of control twitch tension. Thereafter, five patients in each group continued with spontaneous recovery and five had antagonism of paralysis by neostigmine, 0.25 mg, and atropine, 0.1 mg, every 5 min. Serum *d*Tc concentrations were determined by radioimmunoassay every 30 min and during recovery.

There was no difference among the three dosage protocols in any of the following variables: total dose of *d*Tc (mg/m²/hr) needed for two hours of paralysis and spontaneous recovery to 10 per cent of control twitch tension; time for recovery of twitch tension occurring spontaneously or during antagonism by neostigmine; or total dose of neostigmine needed during antagonism of paralysis. There was a relationship between serum *d*Tc concentration and neuromuscular blockade, which was the same among the three dosage protocols. There was no clinically significant difference in pharmacokinetics among the groups.

The authors conclude that there is a relationship between serum *d*Tc concentration and neuromuscular blockade, and that it is independent of *d*Tc dosage administered. Duration of neuromuscular blockade following *d*Tc administration was related to serum *d*Tc concentration and not to initial *d*Tc dosage. (Key words: Antagonists, neuromuscular relaxants: neostigmine. Neuromuscular relaxants: *d*-tubocurarine, pharmacokinetics; pharmacodynamics.)

SINCE THE INTRODUCTION of neuromuscular blocking drugs, partial residual paralysis has been a potentially lethal postoperative complication.[1] One might assume that if lesser amounts of relaxant were administered intraoperatively, postoperative residual paralysis would be less likely to occur. The means for achieving this desirable end are a matter of dispute. Feldman advocates doses of nondepolarizing relaxants larger than those necessary for adequate paralysis.[2] He suggests that duration of paralysis from neuromuscular blockade is a function of 1) the binding of relaxant to the myoneural junction and 2) the dislodgement of relaxant by acetylcholine. He further suggests that no direct relationship needs to exist between blood levels of relaxant and the extent of paralysis. The latter suggestion is supported by results of experiments, in which *d*-tubocurarine (*d*Tc), 3 mg, was diluted in 20 ml saline solution and injected intravenously into an arm isolated from the general circulation by a tourniquet.[3] Paralysis developed in a few minutes, after which time the tourniquet was released. Subsequent perfusion of the arm with blood containing essentially no *d*-tubocurarine did not rapidly reverse the paralysis.

From these results, Feldman believes a strong affinity between muscle relaxant and receptor, rather than blood flow, produces the rate-limiting step in recovery from paralysis. Consequently, Feldman argues that a single large bolus of relaxant given at the start of anesthesia will produce prolonged, adequate paralysis with a relatively low serum concentration of relaxant at the end of anesthesia. In contrast, he suggests that frequently repeated small doses of relaxant that are just sufficient to produce adequate paralysis will result in higher postoperative serum concentrations of relaxant. He believes that the latter approach is more likely to lead to residual postoperative paralysis with its attendant potential for respiratory complications.[2]

In contrast, Matteo *et al.* found a direct correlation between serum *d*Tc concentration and neuromuscular blockade during recovery from paralysis. In addition, they found no difference in serum *d*Tc concentrations necessary for neuromuscular blockade following single doses of *d*Tc of different amounts. Thus, they place a stronger emphasis on the serum concentration–effect relationship than does Feldman.[4]

Furthermore, Waud demonstrated that Feldman's

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Received from the Departments of Anesthesia, Pharmacology, Laboratory Medicine, and Medicine, University of California, San Francisco 94143, and the Department of Anesthesia, Columbia University, New York, New York 10027. Accepted for publication October 17, 1978. Supported in part by Anesthesia Research Center USPHS Grant #GM 15571-11 and USPHS Grant GM 09069. This paper won first prize in the 1978 American Society of Anesthesiologists Resident Research Contest and was presented at the Annual Meeting of the ASA in Chicago, October 21–25, 1978.

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0003-3022/79/0600/0528 $00.80

TABLE 1. Durations and Antagonism of Neuromuscular Blockade and Total *d*Tc Dosage Variables in the Three Study Groups

	Number (per Group)	*d*Tc Dosage Schedule		
		Infusion	5 mg/m²	20 mg/m²
Total dose of *d*Tc (mg/m²) administered in 2 hr	10	18.6 ± 1.4*	22.2 ± 0.9	23.5 ± 0.8
Total dose of *d*Tc (mg/m²/hr) to 10 per cent spontaneous recovery after 2 hr	10	9.2 ± 0.7	10.4 ± 1.0	10.6 ± 0.5
Time (min) from last dose of *d*Tc to 10 per cent spontaneous recovery of twitch tension	10	0†	54 ± 6†	80 ± 12†
Time (min) from last dose of *d*Tc to 60 per cent spontaneous recovery of twitch tension	5	62 ± 10†	126 ± 26†	181 ± 22†
Time (min) for recovery of twitch tension from 10 to 60 per cent after neostigmine	5	17 ± 4	20 ± 1	20 ± 2
Total dose of neostigmine (mg/m²) for antagonism from 10 to 60 per cent recovery of twitch tension	5	0.59 ± 0.11	0.63 ± 0.05	0.61 ± 0.11

Values are means ± SE.
* $P < .01$ infusion < 5 mg/m² and 20 mg/m².
† $P < .01$ infusion < 5 mg/m² < 20 mg/m².

data from the isolated-arm study could be explained by changes in *d*Tc concentration in the extra-cellular fluid.[5] Specifically, she showed that the recovery of neuromuscular function after release of the tourniquet could be explained by washout of *d*Tc from the extracellular fluid as blood flow to the muscle is reestablished. The serum *d*Tc concentrations, had they been measured, would have reflected these changes in extracellular fluid.

These contrasting approaches to relaxant administration (single large dose versus several small doses) all have their clinical advocates. Which approach actually produces the lower serum concentration of muscle relaxant is not known. The present study has supplied these missing data and correlated serum relaxant concentration with the return of neuromuscular function. Specifically, we determine whether the method of *d*Tc administration (continuous infusion, small repeated doses, or large single bolus dose) has any effect on the pharmacokinetics and pharmacodynamics of *d*Tc in anesthetized man. We also determined whether the method of relaxant administration has any effect on antagonism by neostigmine.

Methods

Thirty patients ASA I–II, were studied intraoperatively after informed consent had been obtained. They were 43 ± 20 (SD) years of age, 70 ± 14 kg in weight, and 1.76 ± 0.22 m² in body surface area. They received diazepam, 0.15 mg/kg, orally 60–90 min prior to anesthesia. Anesthesia was induced with halothane and nitrous oxide, 60 per cent. The trachea was intubated without the use of other drugs. Ventilation was controlled to maintain Pa_{CO_2} at 35–45 torr. Anesthesia was maintained with an end-tidal concentration of halothane (ultraviolet analysis) of 0.5–0.7 per cent and nitrous oxide, 60 per cent. Supramaximal square-wave bipolar pulses of 0.15-msec duration were delivered to the ulnar nerve at the wrist through 27-gauge thin-walled electrodes at a rate of 0.15 Hz. The resultant force of thumb adduction was measured with a Grass FT 10 force transducer and recorded on a polygraph.

After the desired end-tidal halothane concentration had been maintained for 20–30 min, *d*Tc was administered intravenously in small repeated doses or a large bolus dose, or by continuous infusion. With all three dosage regimens, 90 per cent or greater depression of twitch tension was maintained for two hours, after which time no further relaxant was administered. Ten patients initially were given *d*Tc, 20 mg/m². Whenever twitch tension recovered to 10 per cent of control before the end of the two-hour study period, an additional 5 mg/m² was administered. At the end of two hours of neuromuscular blockade, spontaneous recovery of twitch tension to 10 per cent of control was permitted in all patients. Ten patients initially were given *d*Tc, 5 mg/m². Additional 5 mg/m² doses were administered when twitch tension recovered to 10 per cent of the control level. Ten patients were given enough *d*Tc to achieve 90 per cent depression of twitch tension. Subsequently, an infusion of *d*Tc was administered to maintain constant 90 per cent neuromuscular blockade for two hours. Subsequently, spontaneous recovery continued in five patients in each group, and in the other five patients in each group, antagonism of neuromuscular blockade was accomplished by administering neostigmine, 0.25 mg, and atropine, 0.1 mg, iv, every 5 min until recovery was complete.

Serum concentrations of *d*Tc were determined by

TABLE 2. Time (Min) for Spontaneous Recovery of Twitch Tension from 10 to 60 Per Cent as Observed and Predicted

Dosage Group	Number	Minutes	
		Observed*	Predicted†
Infusion	5	62 ± 10	71
5 mg/m²	5	84 ± 23	77
20 mg/m²	2	98 ± 30	78
20 mg/m² + extra dose	3	100 ± 26	85

Values are means ± SE.
* All observed $P > .05$ (ANOVA).
† All predicted *vs.* observed $P > .05$ (t test).

radioimmunoassay[6] from peripheral venous blood samples taken 3, 6, 12, 24, 30, 60, 90, and 120 min after the initial administration of *d*Tc in the large-bolus-dose group and at 30, 60, 90, and 120 min in the other two groups, and during recovery of neuromuscular function at 10, 30, and 60 per cent of control twitch tension.

Total dose of *d*Tc administered, rate of recovery of neuromuscular function during spontaneous recovery and antagonism and total dose of neostigmine needed for antagonism were compared among the three methods of *d*Tc administration by analysis of variance.

The relationship of serum *d*Tc concentration and neuromuscular blockade (pharmacodynamics) was analyzed. Only depression of twitch tension between 10 and 90 per cent was used, since "tailing" occurred beyond these limits, making linearization of the concentration–effect relationship difficult. Values obtained during antagonism of blockade by neostigmine were not included. A logistic model for the serum concentration–effect relationship was used.[7] Effect, on a 0–100 per cent scale, equals

$$\frac{100\ e^{Ax+B}}{1 + e^{Ax+B}}$$

where x is the serum *d*Tc concentration and A and B are constants. When the equation is rearranged,

$$\ln\left(\frac{E}{100 - E}\right) = Ax + B$$

where E = effect (twitch tension depression). Regression of ln (E/100 − E) on x has slope A and intercept B. In fact, regression of *d*Tc concentration on twitch depression, not vice versa, was performed because the data arise from controlling depression of twitch tension instead of *d*Tc concentration. The regression parameters (A and B) for the *d*Tc concentration–effect relationships of the three protocols were compared and the statistical significance of any difference tested by using the General Linear Test.[8]

Pharmacokinetic analysis of the serum *d*Tc concentration data was based on the three-compartment model of Gibaldi.[9] The *d*Tc concentrations obtained in this study were compared with those predicted for the dose given by the Gibaldi model. In a previous study using this approach, a scale factor adjustment for volume of distribution from 72 to 97 ml/kg was found necessary when this model is used.[10] A similar scale factor adjustment was made in this study. To test whether the kinetics were the same among the three *d*Tc dosage protocols, we compared the parameters (slopes) of the separate linear regressions of observed *vs.* predicted *d*Tc concentrations, forced through zero, again using the General Linear Test.[8]

Using the appropriately scaled Gibaldi model, the serum *d*Tc concentration for average doses given in each protocol was estimated. By adding the logistic relationship between *d*Tc concentration and twitch tension depression previously determined (see above), we predicted the time of recovery of neuromuscular function. This prediction was compared with the average observed time by analysis of variance.

Results

Less *d*Tc was administered with the continuous-infusion protocol than with the 5 mg/m² and 20 mg/m² protocols (table 1). No dosage difference existed between the latter two protocols. When the dosage of *d*Tc was normalized to a common duration of neuromuscular blockade, *e.g.*, 10 per cent spontaneous recovery of twitch tension after two hours, there were no differences among the three dosage protocols (table 1).

The times from administration of the last dose of *d*Tc to spontaneous recoveries of 10 and 60 per cent of twitch tension were different among the three dosage protocols, being greatest for the 20 mg/m² dose, less for the 5 mg/m² dose, and least for the infusion method (table 1). The times for spontaneous recovery from 10 to 60 per cent of twitch tension (rates of recovery) were not statistically significantly different among the three groups (table 2). Neither the times for recovery of twitch tension from 10 to 60 per cent of control during antagonism with neostigmine nor the doses of neostigmine necessary differed among the dosage groups (table 1). The relationships between depression of twitch tension and serum *d*Tc concentration were not different among the three dosage protocols (fig. 1).

The correlations between observed serum *d*Tc concentration and that predicted by the Gibaldi model

varied among the dosage groups (fig. 2). The pooled data for all protocols revealed an average ratio of observed to predicted of 0.75, corresponding to a volume of distribution of 96 ml/kg. Among the three dosage protocols the relationship of predicted to observed *d*Tc concentration for the 20 mg/m² group differed from those of the 5 mg/m² and infusion groups ($P < .05$). The average ratio of observed to predicted serum *d*Tc concentrations was 0.86 for the 20 mg/m² group, corresponding to a volume of distribution of 83 ml/kg, and 0.69 for the other groups, corresponding to a volume of distribution of 103 ml/kg.

Analysis of the average serum *d*Tc concentration profiles with time for the three dosage protocols indicates that the predicted and observed times for spontaneous recovery of twitch tension were not significantly different (fig. 3, table 2). The Gibaldi model predicts that the rate of decline of serum levels should decrease, and therefore time of spontaneous recovery of twitch tension should increase, with increasing prior dosage of *d*Tc. While the observed values followed this trend, the inter-individual variability in recovery times was so large as to preclude finding a significant difference (table 2).

Discussion

Significantly less *d*Tc was administered with the infusion than with either of the bolus-administration groups, although the differences were too small to be of clinical relevance. Furthermore, when the *d*Tc doses per hour were calculated for the time from the initial dose to spontaneous recovery of 10 per cent of twitch tension after the two-hour study period, there was no difference among the three dosage protocols. None of these findings supports Feldman's concept of *d*Tc–receptor affinity being the primary determinant of duration of neuromuscular blockade.[2,3]

The finding that the times from last *d*Tc administration to 10 and 60 per cent recoveries of twitch tension were longer with the 20 mg/m² dose regimen than the 5 mg/m² regimen, which in turn was asso-

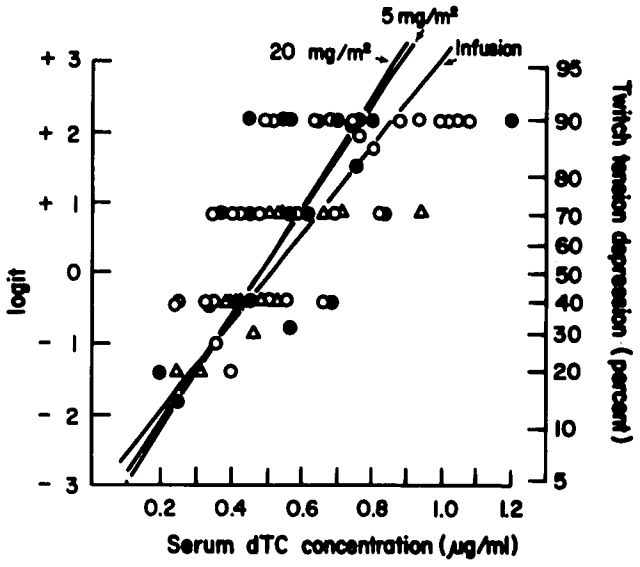

FIG. 1. Linear regression of serum *d*Tc concentration (µg/ml) on logit of twitch tension depression (percentage) in the three dosage groups: ○ = 20 mg/m² (r = 0.67); ● = 5 mg/m² (r = 0.67); △ = infusion (r = 0.79). These regressions were not significantly different ($P > .05$).

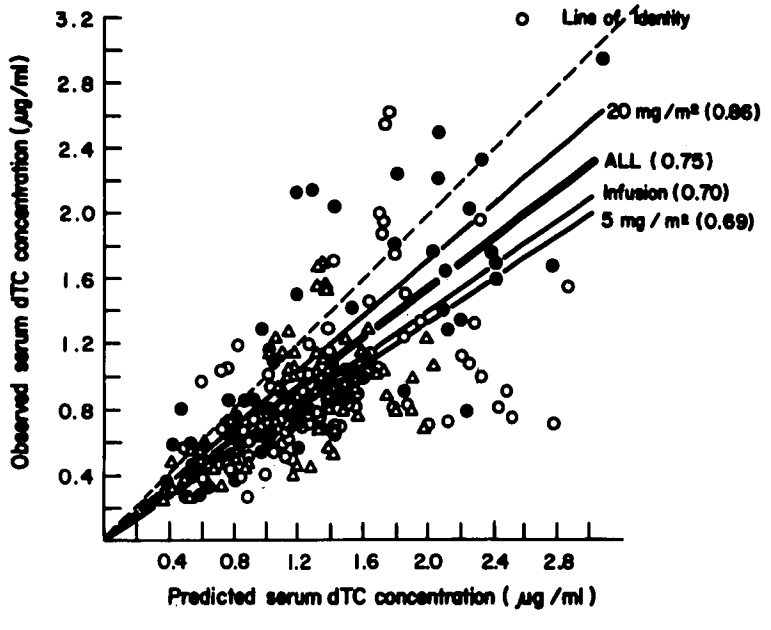

FIG. 2. Linear regression, forced through zero of observed serum *d*Tc concentration (µg/ml) on that predicted by the Gibaldi model in the three dosage groups: ○ = 20 mg/m² (r = 0.85); ● = 5 mg/m² (r = 0.53); △ = infusion (r = 0.59). The line of identity signifies a perfect fit with the Gibaldi model using a volume of distribution (V_d) of 72 ml/kg. The numbers in parentheses indicate the slope of the line and therefore the average ratio of observed to predicted *d*Tc concentration for each group. There is a significant difference between these ratios for the 20 mg/m² *vs.* the other two groups ($P < .05$).

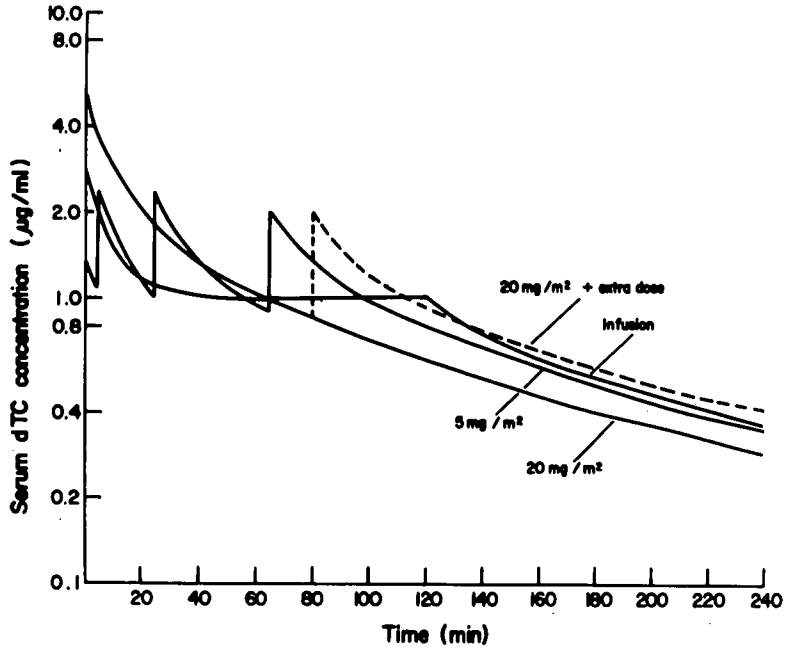

FIG. 3. Simulation of average serum *d*Tc concentration (μg/ml) *vs.* time (min), as predicted by the Gibaldi model, for the average dosage regimens in the different dosage groups. These curves were generated from the average dosage and time for each group using the Gibaldi model adjusted to a volume of distribution of 96 ml/kg. When all three curves are normalized to the serum *d*Tc concentration giving 90 per cent depression of twitch tension as determined in figure 1, the time to spontaneous recovery of twitch tension can be predicted.

ciated with longer times than the infusion regimen, could be explained by a relative "overdose" phenomenon. With the infusion protocol, twitch tension depression was maintained exactly at 90 per cent by varying the *d*Tc infusion rate, whereas for those receiving multiple doses, twitch tension depression was frequently greater than 90 per cent, and was often 100 per cent, for various periods of time after a dose. Clinically this might become important during antagonism of neuromuscular blockade with anticholinesterase agents, since depression of twitch tension of more than 90 per cent takes longer to antagonize[11] and sometimes cannot be antagonized.[12,13]

The rates of recovery of neuromuscular function after *d*Tc administration, as indicated by the times for the twitch tension to increase from 10 to 60 per cent of control, did not differ among groups. This was true both for spontaneous recovery and for recovery augmented by neostigmine (tables 1 and 2). If anything, the patients given constant infusions recovered more rapidly. Furthermore, the doses of neostigmine needed to antagonize paralysis were similar among the groups. Thus, small repeated doses are not more likely to leave a residual relaxant effect postoperatively than is a single large dose.

We found, as others have,[4,14] a relationship between serum *d*Tc concentration and depression of twitch tension (fig. 1). Although variable, serum *d*Tc concentrations associated with any depression of twitch tension correlated by a logistic function. That the *d*Tc dosage schedule had no effect on this relationship again suggests that *d*Tc–receptor affinity is not the primary determinant of duration of neuromuscular blockade.

The three-compartment pharmacokinetic model of Gibaldi adequately predicted the serum *d*Tc concentrations for the three dosage protocols in this study (fig. 2). We found, however, that the model underpredicted the volume of distribution by approximately 25 per cent for the combination of all groups, as it had in a previous study from our laboratory.[10] The relationships between observed and predicted concentrations differed among the three dosage protocols only within a scale factor, the volume of distribution, with 83 ml/kg being obtained for the 20 mg/m² group and 103 ml/kg for the 5 mg/m² and infusion groups. This finding differs from that of Wingard and Cook, who found an apparent increase in the volume of distribution when comparing *d*Tc doses of 0.3 mg/kg and 0.6 mg/kg.[14] We are unable to explain this difference. In any event, the differences in the volumes of distribution observed in this study were small and not clinically significant.

There was little difference of serum *d*Tc concentrations with time among the three dosage groups (fig. 3). If anything, the patients given repeated small doses or continuous infusions had lower concentrations with time. These findings do not support Feldman's prediction of a lower serum relaxant concentration with a large-dose technique.[2] Furthermore, these slight differences in *d*Tc concentrations with time had an insignificant effect on the rates of decrease of serum *d*Tc concentrations after the last dose was administered (table 2).

In summary, there is no clinically significant difference in the pharmacodynamics, pharmacokinetics, and spontaneous reacovery or antagonism of neuromuscular blockade with markedly different *d*Tc dosage schedules. However, the use of small, frequent doses or continuous infusion of relaxant while monitoring neuromuscular function with a peripheral nerve stimulator may have advantages over the large-bolus technique. For example, the duration of neuromuscular blockade needed for a surgical procedure is not always predictable in advance; the large-dose technique may result in 100 per cent blockade, which cannot always be antagonized with anticholinesterase agents; and the extent of neuromuscular blockade can be varied more readily with changing surgical needs.

The authors acknowledge the assistance of Edmond I. Eger, II, M.D., and Laurie Wender, M.A., in the preparation of this manuscript.

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