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Stimulus Frequency and Dose–Response Curve to d-*Tubocurarine in Man*

Hassan H. Ali, M.D., and John J. Savarese, M.D.**

The relationship of the frequency of motor-nerve stimulation to the dose–response to *d*-tubocurarine was studied in 45 adult patients during nitrous oxide–oxygen–morphine–thiopental anesthesia. One of five stimulus frequencies, 0.1, 0.15, 0.25, 0.5, and 1.0 Hz, was employed in each of five groups of nine patients. Cumulative dose–response curves for inhibition of evoked thumb adduction were constructed at each frequency on log probit scales and the ED_{50} and ED_{95} values were determined. The apparent potencies of *d*-tubocurarine at 0.5 and 1.0 Hz were significantly different from that at 0.1 Hz; for example, at 0.1 Hz the ED_{50} and ED_{95} were 0.25 and 0.52 mg/kg, respectively. The corresponding values at 1.0 Hz were 0.07 and 0.15 mg/kg, respectively, or approximately 3.5 times less. The durations of recoveries of the twitch from 5–25 per cent of control at 1.0 and 0.5 Hz were 13 ± 2 min (mean ± SE) and 20 ± 2 min, respectively. These durations were significantly different from that at 0.1 Hz (30 ± 2 min). These results emphasize the importance of defining the stimulus frequency for meaningful interpretation of the dose–response relationships for nondepolarizing relaxants in man. Slow stimulus rates (0.1–0.15 Hz) are most useful clinically, since all levels of clinical relaxation can be achieved at these rates without abolishing the evoked twitch response. (Key words: Measurement techniques: neuromuscular blockade. Monitoring: stimulator, nerve. Neuromuscular relaxants: *d*-tubocurarine.)

IT HAS LONG BEEN KNOWN that the frequency of motor-nerve stimulation influences the evoked twitch response following administration of *d*-tubocurarine and other nondepolarizing relaxants to animals[1,2] and man.[3,4] These studies showed that the faster the rate of stimulation, the greater the apparent neuromuscular blockade. Recently, quantitative studies of the dose–response relationships of neuromuscular blocking drugs have been undertaken in man.[5–8] However, standardization of the frequency of motor-nerve stimulation has not been attempted. Some investigators used twitch frequencies ranging from 0.1 to 5.0 Hz.[5–12] Others used repeated tetanic stimulation, *e.g.*, 20 Hz[13] or 50 Hz,[6,11] or did not specify the frequency of stimulation, or used a BlockAid® monitor.[14–17]

Discrepancies in dose–response results obtained in previous investigations and the authors' personal experience in two earlier studies[5,8] prompted us to investigate quantitatively the influence of the frequency of ulnar-nerve stimulation on the dose–response to *d*-tubocurarine (*d*Tc) in man and to determine the clinical relevance of the ED_{95} at each frequency selected.

Methods

Forty-five adult surgical patients, ASA class I–II, 43 ± 2 years of age, weighing 66 ± 2 kg (mean ± SE) were studied. They were divided into five groups of nine patients each. All were free of neuromuscular or endocrine disease and gave informed consent for the study. Morphine sulfate, 0.15 mg/kg, and scopolamine hydrobromide, 0.005 mg/kg, were administered intramuscularly one hour prior to induction. Anesthesia was induced with thiopental, 3–5 mg/kg, and maintained with a nitrous oxide and oxygen mixture (4:2 l/min) via a face mask in a semiclosed circle absorber system. In addition, increments of thiopental and morphine or fentanyl were given intravenously to maintain a stable level of light anesthesia in the absence of surgical stimulation. The ulnar nerve was stimulated at the wrist via two 22-gauge steel needle electrodes placed subcutaneously. Supramaximal square-wave pulses of 0.2-msec duration were delivered to the nerve using a Grass S88 stimulator through an SIU5 isolation unit. Five stimulus frequencies were studied: 0.1, 0.15, 0.25, 0.5, and 1.0 Hz. The hand and forearm were immobilized on a special arm board, described elsewhere.[18] Only one stimulus frequency was employed in each group. Evoked thumb adduction was measured using a Grass FT-10 force transducer. Recordings were made on a Grass polygraph.

After establishment of a stable control twitch response, incremental doses of *d*Tc were administered. Respiration was either assisted or controlled manually as necessary to maintain an end-tidal P_{CO_2} in the range of 35–45 torr. At 95–99 per cent twitch suppression, and following an additional dose of thiopental (75–100 mg), conditions for laryngoscopy and attempted tracheal intubation were evaluated (by an evaluator who was unaware of the frequency of stimulation used) on a scale of 3, with 1 being good to excellent (relaxed jaw, vocal cords separated, and little or no coughing in response to intubation); 2 being fair (difficulty in opening the jaw, moderate vocal cord movement, and coughing in response to tracheal intuba-

* Assistant Professor of Anesthesia, Harvard Medical School; Associate Anesthetist, Massachusetts General Hospital.

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Address reprint requests to Dr. Ali.

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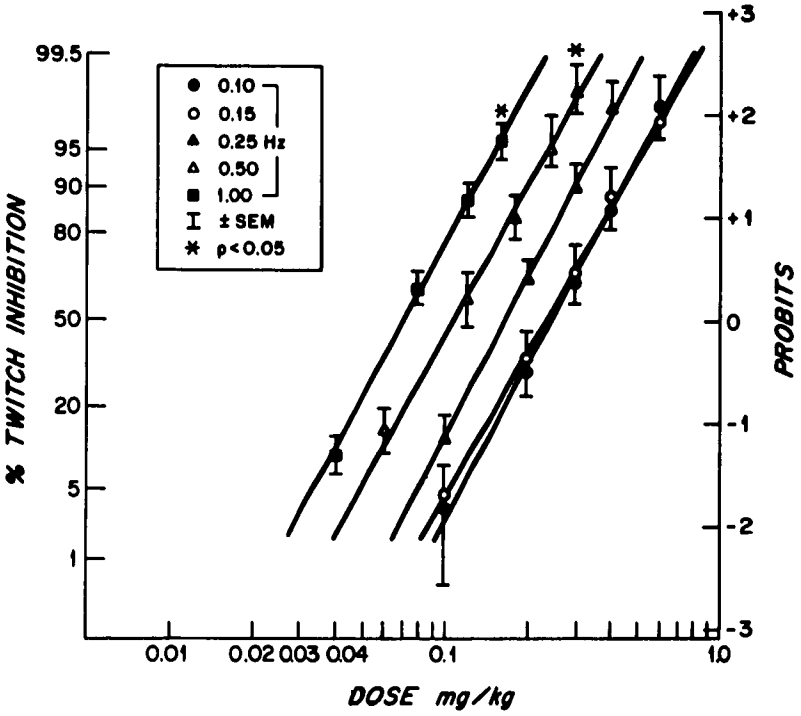

FIG. 1. Comparative mean cumulative dose–response curves for *d*-tubocurarine at the five stimulus frequencies indicated. Each curve indicates the mean of the individual dose–response curves determined for each of the nine patients in each frequency group. The curves do not deviate significantly from parallelism. The potencies at 0.5 and 1.0 Hz are significantly different from that at 0.1 Hz ($P < 0.05$).

tion) and 3 being inadequate to impossible (the jaw could be opened only with considerable difficulty, and the vocal cords were tightly adducted). The additional dose of thiopental was given routinely prior to intubation to decrease the possibility of awareness during intubation.

Four or five incremental doses of *d*Tc were given to each patient over a period of 8–12 min in a manner described elsewhere.[5] The size of the incremental dose of *d*Tc varied with the frequency of stimulation studied. This approach was adopted from past experience in order to be able to obtain three or four data points necessary to construct a dose–response curve. Three different incremental doses were used: 0.04 mg/kg for the 1.0-Hz group, 0.06 mg/kg for the 0.5-Hz group, and 0.1 mg/kg for the other three groups, 0.25, 0.15, and 0.1 Hz. Cumulative dose–response curves were constructed at each stimulus frequency on log probit scales. Goodness of fit of the data to a straight line was evaluated by the χ^2 test, and parallelism of the dose–response curves was tested using the method of Litchfield and Wilcoxon.[19] The durations of recoveries from 5–25 per cent of control at different frequencies were compared by use of the Student *t* test. $P < 0.05$ was regarded as significant.

Results

As the frequency of stimulation was increased, the dose–response curve shifted to the left (fig. 1). Goodness of fit of the data to straight lines on log probit coordinates was significant by χ^2 test, and the curves did not deviate significantly from parallelism. The apparent potencies of *d*Tc at 0.5 and 1.0 Hz *vs.* 0.1 Hz were significantly different. The ED_{50} and ED_{95} values were approximately 3.5 times greater at 0.1 Hz than at 1.0 Hz (table 1). At stimulus frequencies of 0.5 and 1.0 Hz, it was difficult to impossible to achieve endotracheal intubation at the ED_{95} value. An additional dose of *d*Tc had to be administered to permit this procedure to be accomplished. This additional dose generally resulted in the total dose being approximately equal to that administered at 0.1 Hz. This resulted in complete abolition of the twitch response. At 0.25 Hz the intubating conditions at the ED_{95} value were fair, while at 0.1 and 0.15 Hz the conditions were good to excellent.

The durations of recoveries of the evoked twitch from 5 to 25 per cent of control (table 2) indicate that at rapid stimulus rates (1.0 Hz) the apparent recovery time was significantly shorter than at 0.1 Hz (13 ± 2 min *vs.* 30 ± 2 min, respectively).

Discussion

Evidence from experimental animals and man indicates that during repetitive neural stimulation, there is a progressive decrease in the amount of acetylcholine (ACh) released from motor-nerve terminals, a decrease reflected in a progressive diminution in the size of the endplate potentials.[20–22] Normally, the quantity of ACh released at motor endplates is more than that

TABLE 1. The ED_{50} and ED_{95} and Their Confidence Limits at the Five Stimulus Frequencies Indicated

	Stimulus Frequency (Hz)				
	0.1	0.15	0.25	0.5	1.0
ED_{50} (*d*Tc, mg/kg)	0.25 (0.16–0.37)	0.24 (0.15–0.36)	0.16 (0.1–0.25)	0.11 (0.07–0.17)	0.07 (0.05–0.11)
ED_{95} (*d*Tc, mg/kg)	0.52 (0.29–0.91)	0.52 (0.29–0.95)	0.35 (0.12–0.87)	0.24 (0.11–0.52)	0.15 (0.07–0.32)

TABLE 2. Durations of Recoveries of Twitch from 5 to 25 Per Cent of Control at the Frequencies Indicated

	Stimulus Frequency (Hz)				
	0.1	0.15	0.25	0.5	1.0
Duration (min ± SE)	30.1 ± 2.1	29.6 ± 3.8	21.7 ± 3.2	19.6 ± 1.7	13.0 ± 1.8
Significance *vs.* 0.1 Hz	—	N.S.	$0.1 < P < 0.05$	$P < 0.005$	$P < 0.001$

necessary for normal muscle contraction, despite the exponential decrease in its release with repetitive neural stimulation. This provides a wide margin of safety for neuromuscular transmission.[23] When the sensitivity of the endplate to ACh is decreased, *e.g.*, by *d*Tc, the muscle fibers just activated by a slow rate of stimulation may fail to fire at a faster rate because the endplate potentials become subthreshold as a result of diminished acetylcholine output at the higher stimulus rate. As a result, some muscle fibers fail to contract, causing a decrease in the evoked twitch height.

In this study, an increase in the frequency of ulnar-nerve stimulation from 0.1 to 1.0 Hz significantly shifted the dose–response curve for *d*Tc to the left. In addition, the recovery time of the evoked twitch from 5 to 25 per cent of the control response was shortened from approximately 30 min at 0.1 Hz to 13 min at 1.0 Hz. In other words, varying the frequency of neural stimulation in the range tested had a significant effect on the apparent potency of *d*Tc and its recovery time. These findings have also been observed with metocurine and pancuronium[5,8] at two stimulus frequencies. It becomes apparent that valid comparison of the results obtained by various investigators studying this group of drugs is difficult because of differences in methodology, particularly those involving stimulus frequency. The variation in the frequencies of motor-nerve stimulation chosen by Hughes *et al.*[6] and Schuh[9] to determine the potency and duration of action of dimethyltubocurarine (metocurine) can explain the differences in the results obtained, *i.e.*, the ED_{95} value of metocurine obtained by Hughes *et al.*[6] was 0.3 mg/kg at 0.08 Hz, while the ED_{95} value of Schuh[9] at 0.2 Hz was 0.1 mg/kg. A similar difference was found in the studies of metocurine done by Donlon *et al.*[5] and Savarese *et al.*[8] where the ED_{95} values were 0.175 mg/kg at 0.25 Hz and 0.28 mg/kg at 0.15 Hz, respectively. The conclusion by another group of investigators[16] that twice as much *d*Tc was required to depress ventilatory musculature as was needed to suppress the evoked twitch response of the thumb could not be accepted as accurate without defining the stimulus frequency used for twitch measurement.[16,24] In the light of the present study, two to four or more times the amount of *d*Tc might be needed to suppress thumb twitch *vs.* ventilatory measurements.

Thus, differing stimulus frequencies can dramatically influence results and conclusions derived concerning the potencies and durations of action of nondepolarizing neuromuscular blocking drugs. The major advantage of using slow frequencies of stimulation (*e.g.*, 0.1–0.15 Hz) is that at these rates, all necessary levels of clinical neuromuscular blockade can be identified without the necessity of abolishing the twitch response. The additional dose of thiopental given prior to laryngoscopy to decrease the possibility of awareness during intubation may have contributed to the success of endotracheal intubation, but by no means compensated for inadequate levels of neuromuscular blockade. As was evident from the results of this study, the ED_{95} values at the frequencies of 1.0, 0.5, and 0.25 Hz were not as reliable an index of satisfactory relaxation for endotracheal intubation as was the ED_{95} value at 0.1 or 0.15 Hz.

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