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Tactile Evaluation of Train-of-four Count as an Indicator of Reliability of Antagonism of Vecuronium- or Atracurium-induced Neuromuscular Blockade

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Recent evidence suggests that edrophonium is not the agent of choice to reverse profound neuromuscular blockade but remains an efficacious drug when the level of neuromuscular blockade to be antagonized is modest. We studied 90 healthy adults in an attempt to address the questions: 1) How much variability in such neuromuscular parameters as single twitch height and the train-of-four (TOF) fade ratio (T4/T1) exist when the TOF count first returns to four palpable responses? 2) Is edrophonium a reliable antagonist at this measured point of recovery? 3) What is the optimal dose of edrophonium needed to produce prompt (< 10 min) and satisfactory (T4/T1 > 0.7) reversal when the fourth response of the thumb to indirect TOF stimulation just becomes palpable? Patients were given a bolus atracurium or vecuronium (n = 45 in each group) followed by an iv infusion sufficient to maintain single twitch as measured by electromyography at 10–15% of control values. At the end of surgery, the infusion was terminated and spontaneous recovery was allowed to begin. Once the tactile TOF count was four, edrophonium 0.3, 0.5, or 0.75 mg/kg was administered. At a count-of-four the first twitch averaged 37% of control (± 8.5% standard deviation; pooled data from all groups) and the mean T4/T1 ratio was 0.14 ± 0.049. After atracurium neuromuscular blockade, edrophonium 0.3 mg/kg produced adequate antagonism in 10 min. At this time the mean T4/T1 ratio was 0.79 ± 0.07 and the lowest observed value was 0.67. Increasing the edrophonium dose to 0.75 mg/kg accelerated recovery by 4–5 min. At a TOF count-of-four after vecuronium administration, edrophonium 0.75 mg/kg produced similar results. However, 0.3 and 0.5 mg/kg of edrophonium resulted in less consistent reversal of vecuronium. In these groups, 2 and 3 individuals respectively had T4/T1 ratios < 0.60 at 10 min postantagonism despite mean values of 0.70. For reversal of residual vecuronium blockade at the point of return of the TOF count to four, therefore, the recommended dose of edrophonium is 0.75 mg/kg. Under similar conditions after atracurium, as little as 0.3 mg/kg of edrophonium will produce reliable antagonism if 10 min is allowed for recovery. (Key words: Monitoring: neuromuscular blockade. Neuromuscular antagonists: edrophonium. Neuromuscular relaxants: atracurium; vecuronium.)

OPINION regarding the place of edrophonium as an antagonist of nondepolarizing neuromuscular blockade has fluctuated widely over the past 25 yr. In 1965 Churchil-Davidson[1] warned of the danger of "recurarization" after the administration of edrophonium, and two years later Katz[2] agreed that edrophonium was an unsatisfactory antagonist of *d*-tubocurarine. In 1979, however, Kopman[3] and Bevan[4] independently confirmed that when edrophonium is used to reverse the effects of pancuronium, antagonism is sustained, and suggested that earlier reports of the ineffectiveness of the drug as an antagonist of nondepolarizing neuromuscular muscle relaxants were derived from studies using inadequate dosage. By 1983, opinion regarding edrophonium had radically changed. In an editorial entitled "A New Look at an Old Drug," Miller and Cronnelly suggested that its "shorter onset and lower atropine requirement probably justify a preference for edrophonium over neostigmine or pyridostigmine as a routine antagonist."[5] In the last 5 yr, however, accumulated evidence suggests that edrophonium is not the agent of choice for reversal when the level of neuromuscular blockade is profound (single twitch < 10–15% of control) or when large doses of long-acting blocking agents have been administered.[6–13]

Despite these recently recognized limitations on the usefulness of edrophonium, it still remains an efficacious drug when the level of neuromuscular blockade to be antagonized is less intense.[14] Cashman *et al.*[15] recently assessed the time for the train-of-four (TOF) ratio to return to 0.75 after after administration of edrophonium 0.5 mg/kg at various degrees of spontaneous recovery from atracurium. When twitch had returned spontaneously to 25% of control (T1/Tc = 0.25, where T1 = height of first of four TOF twitches and Tc = control twitch height), the mean recovery time after edrophonium was 5.6 min with a range of 1–15 min. When the T1/Tc ratio had returned to 0.50, the mean recovery time was only 1.1 min (range 0.7–4.0 min). Unfortunately, in view of the unreliability of subjective assessment of indirectly evoked responses to ulnar nerve stimulation,[16] one may reasonably question the utility of this sort of information, since most anesthesiologists rarely have access to equipment that can quantitate the extent of single-twitch recovery.

However, Lee found that when the fourth evoked twitch (T4) could be discerned visually, T1 had recovered to 25% of control,[17] and O'Hara *et al.*[18] reported that a TOF count-of-four was associated with 30–40% recovery of single twitch height. Extrapolation from the regression analysis of Ali *et al.*[19] also predicts reappearance of a fourth twitch once the T1/Tc ratio is approximately 0.35. Hence, it is possible that reappearance of the fourth

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evoked response to TOF stimulation may represent a reproducible subjective end-point. I performed the following study to test this hypothesis and to assess if tactile evaluation of the TOF count was a reliable indicator of ease of antagonism from vecuronium- or atracurium-induced neuromuscular blockade using various doses of edrophonium as the reversal agent.

Materials and Methods

Ninety ASA physical status 1 or 2 adult patients (age 18–75 yr) undergoing elective surgical procedures for which the administration of a muscle relaxant was appropriate were included in the study. All patients were free from neuromuscular disease and were within 15% of ideal body weight. The protocol was approved by our hospital's Human Subject Review Committee. Anesthesia was induced with thiamylal sodium 4–5 mg/kg iv and maintained with inhalation of nitrous oxide and halothane (0.50–0.75% end-tidal concentration) plus intravenous fentanyl supplementation as needed. Ventilation was controlled and end-tidal carbon dioxide tension was maintained between 32 and 38 mmHg.

The indirectly evoked integrated compound action potential of the adductor pollicis muscle to supramaximal stimulation of the ulnar nerve at the wrist was measured and recorded using a Datex® 221 NMT monitor. Supramaximal nerve stimulation was achieved using the nerve stimulator incorporated into the Datex unit (pulse width 100 ms, constant current, range 0–70 mA). The test hand was immobilized, and approximately 200–300 g of resting tension was applied to the thumb. Anesthesia was induced, and before any muscle relaxants were administered, Tc and TOF fade ratio (T4/T1) were established after a 5-min period of baseline stabilization. TOF stimulation was given every 20 s during the period of observation, and single-twitch depression, indicated by T1/Tc, and TOF fade were continuously recorded. Six consecutively selected groups were studied.

Group 1: Atracurium plus Edrophonium 0.3 mg/kg (n = 15)

Atracurium 0.3 mg/kg was administered as an intravenous bolus. When twitch depression was maximal, the patient's trachea was intubated, and an infusion of atracurium ($5\ \mu g \cdot kg^{-1} \cdot min^{-1}$) was begun. The infusion was then adjusted to provide 85–90% twitch depression for the remainder of the case. The duration of all infusions exceeded 60 min. When the need for surgical relaxation was over, the infusion was discontinued and spontaneous recovery was allowed to proceed.

At frequent intervals during the recovery period, an observer (a 1st- or 2nd-yr resident in anesthesiology) was asked to manually abduct the monitored thumb slightly and to report the number of responses to TOF stimulation that could be detected by palpation. The observer was unaware of the actually measured T1/Tc or T4/T1 ratios during this period. As soon as the observer was "reasonably certain" that a fourth twitch existed, atropine 6 μg/kg and, 30 s later, edrophonium 0.3 mg/kg were administered intravenously. T1/Tc and T4/T1 ratios were recorded continuously for the next 10 min. If the T4/T1 ratio did not recover to a value greater than 0.85, additional edrophonium was administered until this value was reached. Due to drift in the electromyographic signal,[20] T1/Tc frequently did not return to baseline. Therefore, the control T1 twitch height was referenced to the maximal T1 value attained once the T4/T1 ratio was > 0.85. For example, assume that the T1/Tc ratio reaches a plateau at 0.85 despite a T4/T1 ratio of 0.90. If the fourth twitch was first detected by palpation at a measured T1/Tc value of 0.30, the reported value for this end point would be 0.30/0.85, or 0.35.

Groups 2 and 3: Atracurium plus Edrophonium 0.50 or 0.75 mg/kg (n = 15 each)

The protocol in these groups was identical to that in group 1 except that antagonism was produced with either edrophonium 0.50 or 0.75 mg/kg.

Group 4: Vecuronium plus Edrophonium 0.3 mg/kg (n = 15)

The protocol was identical to that in group 1 except that neuromuscular blockade was induced with vecuronium 0.05 mg/kg and the initial infusion rate was set at 0.9 μg/kg/min.

Groups 5 and 6: Vecuronium plus Edrophonium 0.50 or 0.75 mg/kg (n = 15 each)

The protocol in these groups was identical to that in group 4 except that antagonism was produced with edrophonium 0.50 or 0.75 mg/kg.

Mean T1/Tc ratios at the point where the fourth evoked response to TOF stimulation was manually detected were calculated for each group and compared using single-factor–factorial analysis of variance and the Scheffé F test for multiple comparisons. Mean T4/T1 and T4/Tc ratios at 2, 5, and 10 min postreversal also were calculated for each group. These values were then compared using one-way repeated measures analysis of variance and the Scheffé F test for multiple comparisons. An unpaired Student *t* test was used to make single comparisons of TOF ratios at various times after antagonism, for example, for group 3 at 10 min *versus* group 6 at 10 min. Observed differences were considered significant when $P < 0.05$. Satisfactory recovery was defined as a measured T4/T1 ratio of 0.70 or greater.

TABLE 1. Demographic Data, Groups 1–6

Group (dose, mg/kg)	n	Age (yr)	Weight (kg)	Gender (Men/Women)	Duration of Infusion (min)
1 (AE 0.3)	15	46.3 ± 16.4	64.3 ± 9.3	1/14	111 ± 40
2 (AE 0.5)	15	47.3 ± 16.5	72.9 ± 11.0	4/11	113 ± 55
3 (AE 0.75)	15	41.9 ± 12.5	63.9 ± 7.2	3/12	111 ± 49
4 (VE 0.3)	15	49.5 ± 13.2	68.6 ± 11.4	2/13	121 ± 74
5 (VE 0.5)	15	44.5 ± 12.0	62.1 ± 9.8	2/13	102 ± 34
6 (VE 0.75)	15	43.9 ± 13.6	61.3 ± 9.9	0/15	104 ± 37

Values are mean ± SD.

AE = atracurium + edrophonium; VE = vecuronium + edrophonium.

Results

Subjective Evaluation of Train-of-four Count

The six groups studied did not differ in age, weight, or the duration of the operative procedure (table 1). During recovery from atracurium (pooled data from groups 1, 2, and 3; n = 45) the fourth mechanical response of the thumb became palpable when the first twitch equalled 34% percent of control (± 6.3% standard deviation, range 20–50%). Mean T1/Tc, T4/T1, and T4/Tc values (the ratio of the height of the fourth TOF twitch to height of the control twitch) in groups 1–3 did not differ significantly from each other (table 2). The mean T4/T1 ratio at this time was 0.16. Since the T4/Tc ratio is the product of T1/Tc and T4/T1, it follows that the fourth mechanical response became detectable when it reached 5.3% of control twitch height (0.34 × 0.16 = 0.053). Mean T1/Tc, T4/T1, and T4/Tc values in groups 4–6 did not differ significantly from each other (table 2).

The height of the fourth twitch relative to control, at the time when all four twitches were detectable, was a consistently reproducible end-point. Values from the three vecuronium groups for the T4/Tc ratio (0.051) at the appearance of the fourth palpable response did not differ from those from the atracurium groups. Ninety percent of responses (all groups, n = 90) were in the range of 2.5–7.5% of control.

In contrast, when the fourth evoked response first became palpable, the height of the first twitch compared with control showed considerable variation. At this point in recovery, the average value for the T1/Tc ratio (pooled data, all groups) was 0.37 ± 0.085 (standard deviation) with a range of 0.20–0.70 (fig. 1). However, the mean T1/Tc ratio was greater in those individuals recovering from vecuronium (0.41 ± 0.047, range 27–70) than in those who received atracurium (0.34), $P < 0.0001$.

Antagonism with Edrophonium

For both the atracurium and vecuronium groups, there was no statistically significant improvement in the speed of antagonism noted between those individuals who received edrophonium 0.3 mg/kg compared with those who received 0.5 mg/kg. Increasing the dose to 0.75 mg/kg, however, produced significant increases in the rate of reversal for both relaxants (table 3).

Mean TOF ratios exceeded 0.75 at 10 min in all groups recovering from atracurium (table 3). All individuals in group 3 had reached a T4/T1 ratio of 0.70 at 10 min, and only one individual each in groups 1 and 2 did not achieve this value (fig. 2–4).

TABLE 2. Single Twitch, Train-of-Four, and Fourth Twitch Compared to Control at the Time when the Fourth Evoked Response to TOF Stimulation was First Palpable

Group (dose, mg/kg)	n	T1/Tc	T4/T1	T4/Tc
1 (AE 0.3)	15	0.340 ± 0.062	0.147 ± 0.039	0.050 ± 0.017
2 (AE 0.5)	15	0.331 ± 0.065	0.171 ± 0.056	0.056 ± 0.021
3 (AE 0.75)	15	0.337 ± 0.066	0.159 ± 0.048	0.053 ± 0.017
4 (VE 0.3)	15	0.397 ± 0.089	0.107 ± 0.030	0.042 ± 0.013
5 (VE 0.5)	15	0.375 ± 0.069	0.147 ± 0.057	0.056 ± 0.025
6 (VE 0.75)	15	0.442 ± 0.102	0.133 ± 0.041	0.056 ± 0.011
Groups 1–3	45	0.336 ± 0.063*	0.159 ± 0.048†	0.053 ± 0.019
Groups 4–6	45	0.407 ± 0.047*	0.129 ± 0.046†	0.051 ± 0.018
All groups	90	0.371 ± 0.085	0.144 ± 0.049	0.052 ± 0.018

Values are mean ± SD.

T1/Tc = single switch; T4/T1 = train-of-four; T4/Tc = fourth twitch compared to control; AE = atracurium + edrophonium; VE = vecuronium + edrophonium.

Groups 1, 2, and 3 do not differ significantly from each other in any respect, nor do groups 4, 5, and 6 differ from each other.

* $P < 0.0001$ (T1/Tc, groups 1–3 *vs.* groups 4–6).

† $P < 0.005$ (T4/T1, groups 1–3 *vs.* groups 4–6).

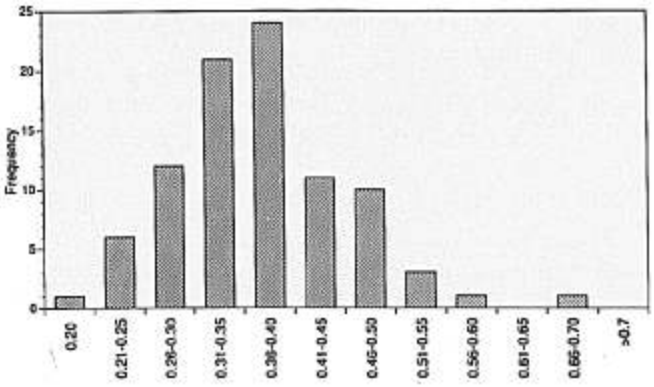

FIG. 1. The height of the first twitch compared to control (T1/Tc) at the time when the evoked train-of-four count had just recovered to four palpable responses.

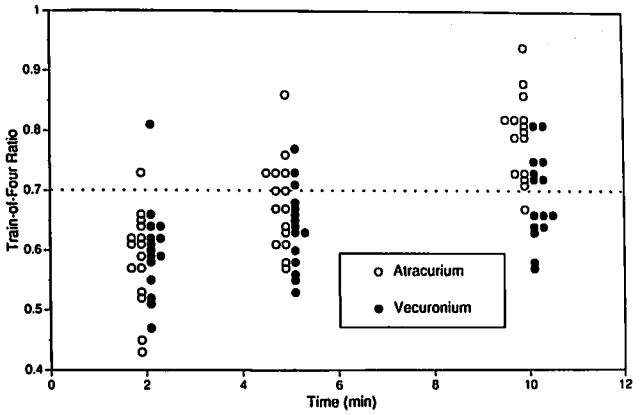

FIG. 2. Train-of-four ratios after edrophonium (0.30 mg/kg) reversal of atracurium or vecuronium when the evoked train-of-four count had recovered to four palpable responses.

Recovery after vecuronium was less predictable at the smaller doses of edrophonium. Mean TOF ratios at 2 min from groups 4–6 equalled or exceeded those found in comparable atracurium groups (table 4). However, in groups 4 and 5, although mean TOF ratios at 10 min approximated a ratio of 0.70, eight and five individuals respectively did not reach this value (figs. 2 and 3). Antagonism of vecuronium with edrophonium 0.75 mg/kg (group 6) was more reliable with mean T4/T1 ratios at 2, 5, and 10 min of 0.77, 0.82, and 0.84, respectively.

Discussion

Subjective Evaluation of Train-of-four Count

Previous investigations of the correlation between twitch height and TOF count either have studied small numbers of patients or have not reported the range of responses observed.[17,18] The results of the present study indicate that when the fourth evoked response to TOF stimulation is first palpable, the mean T1 value was 37 ± 8.5% (standard deviation) of control with a range of 20–70% (fig. 1). In contrast to the large variability in single twitch height found at a threshold TOF count-of-four, the height of the fourth twitch compared to control at this time was quite constant. Mean values were 5.2 ± 1.8% (standard deviation) of control with a range of 2–13%.

In 1975, Lee[17] measured the mechanical response of the adductor pollicis while looking for visible movement in the other fingers of the hand. He suggested that after the administration of *d*-tubocurarine, at 25% recovery of T1/Tc, all four evoked responses of the fingers to TOF stimulation became detectable. Although this figure has been cited widely, in his study of 34 individuals no indication of the variability of this observation is reported. In 1986, O'Hara *et al.*[18] compared the isometric contraction of the thumb (mechanomyogram) in 20 patients with visually observed movements in the contralateral thumb. During recovery from vecuronium, the TOF count returned to four at a T1/Tc ratio of between 0.30 (enflurane anesthesia) and 0.41 (nitrous oxide-narcotic anesthesia).

TABLE 3. Train-of-four Ratios After Antagonism with Edrophonium

Group (dose, mg/kg)	n	2 min	5 min	10 min
1 (AE 0.3)	15	0.59 ± 0.020	0.68 ± 0.020	0.79 ± 0.020
2 (AE 0.5)	15	0.63 ± 0.022	0.71 ± 0.022	0.81 ± 0.019
3 (AE 0.75)	15	0.71 ± 0.022	0.80 ± 0.020	0.87 ± 0.015
4 (VE 0.3)	15	0.60 ± 0.020	0.64 ± 0.018	0.69 ± 0.019
5 (VE 0.5)	15	0.64 ± 0.026	0.68 ± 0.028	0.70 ± 0.024
6 (VE 0.75)	15	0.77 ± 0.017	0.82 ± 0.019	0.84 ± 0.020

Values are mean ± SE.

AE = atracurium + edrophonium; VE = vecuronium + edrophonium.

Edrophonium administered when the evoked train-of-four count had recovered to four palpable responses.

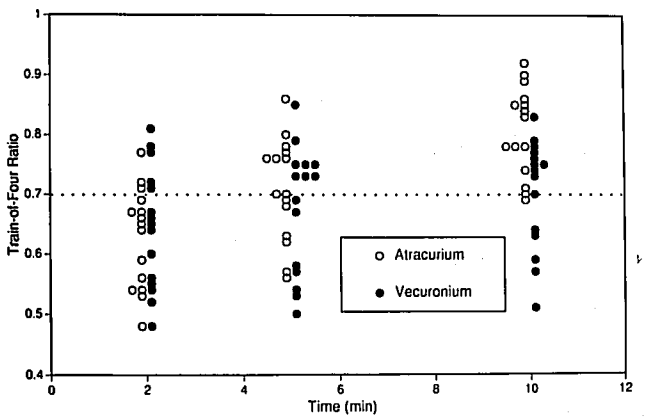

FIG. 3. Train-of-four ratios after edrophonium (0.50 mg/kg) reversal of atracurium or vecuronium when the evoked train-of-four count had recovered to four palpable responses.

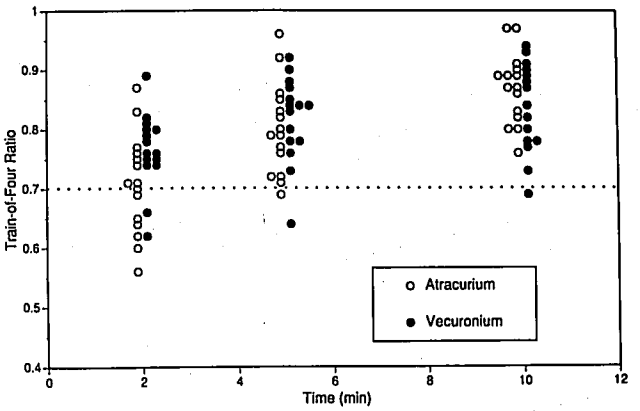

FIG. 4. Train-of-four ratios after edrophonium (0.75 mg/kg) reversal of atracurium or vecuronium when the evoked train-of-four count had recovered to four palpable responses.

Viby-Mogensen[21] suggests that tactile evaluation of thumb reaction after ulnar nerve stimulation is the best way to evaluate muscle force. Nevertheless, there have been no reports correlating tactile estimation of TOF count and simultaneously measured single twitch response of the adductor pollicis, in part because of technical problems. It is difficult, for example, to measure the MMG and tactile response at the same time, since accurate mechanical recordings of T1/Tc require a constant preload. However, EMG recordings of the adductor pollicis compare quite well with MMG readings[22]; hence the current study permitted simultaneous evaluation of subjective and objective responses from the same muscle. The current results for vecuronium (T1/Tc = 0.41 at a TOF count-of-four) are quite similar to those of O'Hara *et al.*[18] despite the differences in methodology.

Pearce *et al.*[23] have reported comparable results. Using MMG recordings they found during recovery that, at a T1/Tc ratio of 0.25, TOF fade ratios for atracurium and vecuronium were 0.06 and 0.02, respectively. At return of T1 to 50% of control, the TOF values were 0.19 and 0.16. Our results indicate that when the T4/Tc ratio approximates 0.05, a weak fourth twitch is first palpable. Hence, the fourth response to TOF stimulation should have become palpable at a T1/Tc value approximately midway between 0.25 and 0.50 in Pearce's study.

I also found that blockade after vecuronium exhibits more fade on recovery than that after atracurium. At the threshold TOF count-of-four, the T4/T1 ratio for vecuronium was only 0.13 compared to 0.16 for atracurium ($P < 0.005$). This difference may appear small, but it should be remembered that the T1/Tc ratio for vecuronium at this time (0.41) was significantly higher than that for atracurium (0.34) ($P < 0.0001$). Erkola *et al.*[24] found that, when the first twitch had returned to 75% of control, the TOF fade ratios for atracurium and vecuronium were 0.35 and 0.23 respectively (n = 30 in each group; $P < 0.001$), confirming greater fade with vecuronium during recovery.

TOF Count of Four as a Predictor of Ease of Reversal with Edrophonium

Atracurium

The results of this investigation suggest that the presence of four palpable twitches of the thumb after indirect TOF stimulation should be a reliable guide to edrophonium dosage after recovery from atracurium- or vecuronium-induced neuromuscular blockade. If prompt and adequate antagonism is defined as return of the TOF fade ratio to a value greater than 0.70 within 10 min, then as little as 0.30 mg/kg of edrophonium may be a satisfactory antagonist of atracurium. Only 1 of 15 individuals in group 1 had a T4/T1 ratio of < 0.70 at this time, and that value was 0.67. Of perhaps greater importance is that once recovery from atracurium had begun, it was always a continuous process, without evidence of "plateau" in the rate of recovery. Although increasing the dose of edrophonium from 0.30 to 0.50 mg/kg did not produce any significant improvement in the speed of recovery, 0.75 mg/kg did result in a substantial decrease in recovery time. In group 3, the mean T4/T1 ratio at 2 min after reversal was 0.71 and the lowest observed individual value at 5 min was 0.69. Hence a 4- to 5-min reduction in the time to a TOF fade ratio of 0.70 may be accomplished at the expense of a 2.5-fold increase in the dose of edrophonium.

Vecuronium

Two patients in group 4 (0.3 mg/kg edrophonium) and three individuals in group 5 (0.5 mg/kg edrophonium) had T4/T1 values of < 0.60 at 10 min postreversal (figs. 1 and 2). Therefore, in contrast to the situation with patients recovering from atracurium, the smallest dose of edrophonium that ensured adequate antagonism after vecuronium-induced neuromuscular blockade was 0.75 mg/kg. After the lower two doses of edrophonium, TOF ratios at 2 min postreversal did not differ between comparable atracurium or vecuronium groups. However, recovery beginning at that point was usually a slower process than that after atracurium. If ease of reversal is related to the rate of spontaneous recovery, then the differences

TABLE 4. Level of Statistical Significance of Observed Differences in Train-of-four Values Postreversal (*P* Values)

Comparison (dose, mg/kg)	2 min	5 min	10 min
AE 0.3 *versus* VE 0.3	NS	NS	<0.001
AE 0.5 *versus* VE 0.5	NS	NS	<0.002
AE 0.75 *versus* VE 0.75	<0.05	NS	NS

AE = atracurium + edrophonium; VE = vecuronium + edrophonium; NS = not significant.

noted between these drugs are not unexpected. Erkola *et al.*[24] studied such parameters of spontaneous return of neuromuscular function as T1/Tc recovery index, T4/T1 recovery index, and the time from T1/Tc of 0.25 to a TOF fade ratio of 0.75. They aptly demonstrated that with atracurium there is little prolongation in any of the indices of recovery as the duration of administration is increased. The opposite is true of vecuronium.

In the current study, after 0.75 mg/kg of edrophonium, the T4/T1 ratio at 2 min was higher in the vecuronium group than in the atracurium group ($P < 0.05$). However, it is likely that this merely reflects the finding that single-twitch height at the moment of reversal was significantly higher in group 6 than in group 3 (T1/Tc ratios of 0.44 *vs.* 0.34 respectively, $P < 0.005$). At 5 and 10 min postreversal there were no differences between these two groups.

The current data suggest that edrophonium requirements are not only a function of the level of spontaneous recovery that has already taken place but also are in part a function of the recovery profile of the neuromuscular blocking agent to be antagonized. Given identical levels of single-twitch recovery, it is likely that, 2–3 min after equal doses of edrophonium are given, similar degrees of reversal will result regardless of the nondepolarizing blocker previously administered.[8] Further return of neuromuscular function depends on a continued reduction in the plasma concentration of blocking agent. In view of the differences found in this study between atracurium and vecuronium, extrapolation of these results to other neuromuscular blockers should be performed with caution. Hence, until evidence to the contrary is available, at the point of return of the TOF count to four responses, the recommended dose of edrophonium for prompt reversal of residual blockade is 0.75 mg/kg for vecuronium. With atracurium, the dose of edrophonium may be reduced to as little as 0.3 mg/kg if one is willing to wait an additional 5 min for satisfactory antagonism.

It must be emphasized that at the threshold return of the fourth twitch to palpation, the fourth twitch was still very weak, and TOF fade was always apparent. Several observers in the study commented that the fourth response frequently was discernible only because it followed three other twitches and "they therefore knew when it was coming." The recommendations of the current report should therefore be considered somewhat conservative. It is probable that once the fourth response to TOF stimulation had been palpable for some period of time, smaller doses of edrophonium would have been equally effective.

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