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Twitch, Tetanus and Train-of-Four as Indices of Recovery from Nondepolarizing Neuromuscular Blockade

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This study was undertaken to compare the sensitivities of the train-of-four response (2 Hz for 2 s), the single twitch (0.15 Hz), and the tetanic response (50 Hz for 5 s) as indices of residual nondepolarizing block. Spontaneous or induced recovery of evoked thumb adduction in response to ulnar nerve stimulation was studied. One hundred and seven adult surgical patients were divided according to the relaxant used, into six groups. We found that when the single twitch recovered to control height, the train-of-four ratio was well below 1.0. This ratio was significantly lower during spontaneous recovery than following neostigmine antagonism of the block ($P < 0.01$). The tetanic response was fully sustained when the train-of-four ratio was above 0.7. When the ratio was less than 0.7, variable degrees of fade of tetanus were evident. Analysis of variance indicated similar train-of-four ratios among the six groups at complete recovery of the single twitch irrespective of the relaxant technique used ($P < 0.1$). It is concluded that a train-of-four ratio of 0.7 or higher reliably indicates the recovery of the single twitch to control height and a sustained response to tetanic stimulation at 50 Hz for 5 s. The clinical significance of this study is as follows: the train-of-four response provides the same indication of clinical recovery from nondepolarizing block as obtained from tetanic stimulation at a physiological frequency; and reliance on the recovery of the single twitch to control height as a criterion of spontaneous return to normal clinical neuromuscular function may be misleading. (Key words: Antagonists, neuromuscular relaxants: neostigmine. Measurement techniques: neuromuscular blockade. Monitoring: stimulator, nerve. Neuromuscular relaxants: *d*-tubocurarine; metocurine; pancuronium. Neuromuscular transmission.)

ASSESSMENT OF MUSCULAR FUNCTION in patients recovering from neuromuscular block is most effective when the subject is awake and cooperative. The measurement of tidal volume and inspiratory force provides useful information in unconscious, spontaneously breathing individuals. Criteria which do not require patient cooperation are measurement of the evoked responses to peripheral motor nerve stimulation during single twitch (0.1–0.15 Hz), tetanic (30–200 Hz), and train-of-four (2 Hz for 2 s) stimulation.[1,2]

Gissen and Katz[3] suggested that the mechanical response to tetanic stimulation at high frequencies (100 and 200 Hz) is a more sensitive index of normal neuromuscular transmission than the single twitch. Epstein and Epstein[4] used electromyography and recommended the use of tetanic stimulation at physiological frequencies (30–50 Hz). Their results suggests that these frequencies are adequate to monitor the state of curarization. Waud and Waud[5] employed a technique to determine receptor occupancy in experimental animals and concluded that the train-of-four (T_4) ratio is slightly more sensitive than the single twitch at 0.1 Hz, and far less sensitive than 100 Hz tetanus for 5 s as an indicator of curarization. However, it has been our clinical impression that the T_4 ratio is much more sensitive than the single twitch and at least as sensitive as tetanus at 50 Hz. We do not believe in the clinical validity of the response to very high frequency tetanic stimulation (*i.e.*, 100 Hz and more) since these frequencies are non-physiologic. We therefore decided to compare the T_4 ratio with fade of tetanic tension at 50 Hz for 5 s, at the times when the single twitch evoked at 0.15 Hz had fully recovered to the control height.

Methods

The protocol was approved by the institutional Committee on Human Studies. One hundred and seven ASA Class I–II surgical patients were studied. They were 44 ± 2 (mean ± SE) years old and weighed 65 ± 1 kg. Informed consent was obtained from each patient. All were free from neuromuscular, circulatory, and endocrine diseases. None had received any drug known to affect neuromuscular function. The subjects were divided into six groups according to the relaxant technique used (table 1). All subjects received diazepam, 0.1–0.15 mg/kg, orally, and/or meperidine, 1–2 mg/kg, intramuscularly, as premedication approximately one hour prior to the induction of anesthesia. Anesthesia was induced with intravenous thiopental (4–5 mg/kg) and maintained with 66 per cent nitrous oxide in oxygen (4L/2L given by mask), together with additional intravenous narcotic analgesics (fentanyl, me-

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peridine or morphine) as needed to maintain a stable balanced anesthetic.

Single supramaximal square wave pulses of 0.2 ms duration at a frequency of 0.15 Hz were delivered to the ulnar nerve at the wrist via two percutaneous 25-gauge steel needle electrodes. A Grass S88 stimulator and a stimulus isolation unit (SIU5) were used. Evoked thumb adduction was transduced and measured using Grass FT-10 force transducer and polygraph in a manner described earlier.[6] A resting thumb tension of 300 g was maintained constant throughout the period of measurement. After establishing a stable control response, one of the relaxants or relaxant combinations were administered in a bolus or in increments to a total dose shown in table 1, achieving 95–99 per cent suppression of the single twitch. Following an additional dose of thiopental and laryngeal spray with 2 ml of 4 per cent lidocaine, endotracheal intubation was performed. Respiration was controlled to maintain an end-tidal P_{CO_2} in the range of 35–45 torr. The single twitch was allowed to recover spontaneously or reversal was induced by atropine and neostigmine (0.02 and 0.04 mg/kg, respectively). Following the return of the single twitch to a stable control height, two or three T_4 stimuli were delivered at 10-s intervals. In 28 patients, tetanus at 50 Hz (T_{50}) for 5 s was applied approximately 30 s following the last T_4. The T_4 ratio was calculated as the ratio of the amplitude of the fourth to the amplitude of the first response in the train and expressed as a percentage. The tetanic response ratio was calculated as the ratio of the amplitude of the response at the end of 5 s and the initial maximal height of the response expressed as a percentage. Analysis of variance was performed to detect possible statistical differences in the patterns of recovery among the nondepolarizing relaxants studied either alone or in combination. Student's *t* tests for paired and unpaired data were used where indicated. Changes were considered significant when $P < 0.05$.

Results

Table 2 shows that when the single twitch had recovered to control height, the train-of-four ratio varied between a mean of 64 per cent in Group VI (pancuronium and *d*-tubocurarine combination) and 74 per cent in Group I (*d*-tubocurarine). Analysis of variance showed that there was no significant difference of the T_4 ratio among the six groups ($P < 0.1$). Regardless of the relaxant received, patients who were allowed to recover spontaneously until the single twitch reached control height showed a significantly greater fade of the train-of-four response (T_4 ratio = 44 ± 5 per cent) than did patients reversed with atropine and neostigmine (T_4 ratio = 68 ± 4 per cent; $P < 0.01$).

TABLE 1. Patients Grouped According to Relaxant Technique

Group	No. of Patients	Relaxant	Dose (mg/kg)
I	24	*d*-Tubocurarine (*d*Tc)	0.5–0.6
II	38	Metocurine (Met)	0.3
III	18	Pancuronium (Pan)	0.1–0.2
IV	7	*d*Tc & Met	0.26 + 0.17
V	7	Pan & Met	0.02 + 0.07
VI	13	Pan & *d*Tc	0.02 + 0.14

TRAIN-OF-FOUR RATIO VS. TETANIC RESPONSE RATIO

Among the 28 patients examined for tetanic response following the response to train-of-four stimulation, 18 demonstrated a fully sustained tetanus (*i.e.*, tetanic response = 100 per cent). This was significantly different from the train-of-four ratio in these patients of 73 ± 2 per cent ($P < 0.01$). In the remaining ten patients, both the train-of-four and tetanic responses showed variable degrees of fade. The train-of-four ratio was 64 ± 3 per cent while the tetanic response ratio was 76 ± 4 per cent ($P < 0.05$).

Discussion

Irrespective of the neuromuscular blocking agent technique used in this study, the T_4 ratio at the point of complete, evoked or spontaneous recovery of the single twitch to control was similar. The T_4 ratio at this point was generally less then the tetanic fade ratio, *i.e.*, more fade was noticeable in the T_4 response than in the tetanic response. The T_4 ratio therefore offers a reasonable alternative to tetanic stimulation at a physiological frequency of 50 Hz for 5 s in assessing adequacy of clinical recovery from nondepolarizing block. Reliance on the single twitch as a criterion of return of normal function may be misleading because a significant degree of

TABLE 2. Train-of-four Ratios for Groups at Full Recovery of Single Twitch

Group	Per Cent T_4 Ratio at Full Recovery of Single Twitch to Control*
I	73.7 ± 1.7
II	67.5 ± 1.8
III	64.9 ± 3.9
IV	67.4 ± 4.7
V	68.9 ± 4.5
VI	63.9 ± 4.3

* Values are mean ± SE.

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receptor occupancy may still be present at this stage, as evidenced by persistent fade of the train-of-four and tetanic responses. This assumes that fade is a measure of the degree of neuromuscular blockade. This has been demonstrated both by evoked mechanical and electromyographic responses.[2,7]

Only one tetanic frequency (50 Hz) was studied because it has been shown that maximal voluntary effort develops the same tension as that artificially evoked by a tetanic stimulus at 50 Hz.[8] Lee and Katz[7] correlated fade of T_4 at 2 and 5 Hz in humans with fade of tetanus at 50 Hz during evoked electromyography. They proposed a substitution of train-of-four for tetanus as a criterion for determining residual nondepolarizing neuromuscular blockade, principally because tetanus, in addition to depleting the immediately available store of acetylcholine, facilitates the neuromuscular response during and following its application. A single tetanus therefore artificially shifts all subsequent neuromuscular events toward normality. In cats, Lee *et al.*[9] studied ten parameters of DTC-induced neuromuscular block and found that the T_4 response at 2 Hz was a more sensitive index of curarization than tetanic fade at 50 Hz for 5 s.

Gissen and Katz[3] suggested that the response to high frequency tetanic stimulation at 100 and 200 Hz for 500 ms is a more sensitive index of curarization than the single twitch at 0.3 Hz. Based on this study, Waud and Waud[10] determined in experimental animals (cat, rabbit and dog) the relation between the single twitch, tetanic response at 30 and 100 Hz, and receptor occlusion. They found that both sustained tetanus at 30 Hz and the return of the single twitch to control height corresponded to 75–80 per cent receptor occupancy by *d*-tubocuraine, while tetanus at 100 Hz was sustained at only 50 per cent receptor occlusion. This study introduced a factor which does not exist in the clinical setting (the repeated use of succinylcholine in the presence of *d*-tubocurarine). Being aware of the possibility of development of desensitization block, the authors administered succinylcholine only at one-hour intervals.[10] Repeated tetanic stimulation was employed. This may produce a local decurarizing effect (an apparent accelerated recovery in the muscle being stimulated) which might not accurately reflect the systemic effect of *d*-tubocurarine and would result in premature recovery of the single twitch[11] and the train-of-four responses locally.§ For this reason, data for tetanic fade must be obtained after T_4 data have been generated. Nevertheless the data of Waud and Waud[10] provide a rationale, on the basis of receptor occlusion percentage, for understanding the patterns of evoked neuromuscular responses. The clinical applicability of the data nevertheless must be reconciled with studies performed in humans under clinical conditions. It would appear that had Waud and Waud studied tetanus at 50 Hz, their laboratory data might have coincided well with the clinical results of the present study.

Whether it is appropriate to stress the neuromuscular junction beyond normal central nervous system function is a relevant clinical consideration. High frequency tetanus increases the average neuromuscular refractory period, suggesting that part of the fade seen is due to a decreased ability of the muscle to respond rapidly during the latter part of tetanus rather than to receptor occlusion.[4] There may be widening as well as diminution of the compound muscle action potential as observed on electromyography during high frequency tetanus.[4] This may lead to an increase in asynchrony of excitation, hence decreasing the force of contraction[12] and possibly increasing the apparent fade. This reasoning is supported by the clinical finding of Stanec *et al.*[13] who showed that 5-s tetanic stimulation at frequencies higher than 70 Hz were not sustained in the absence of neuromuscular blocking drugs in patients anesthetized with nitrous oxide-oxygen-thiopental and narcotics. It might be concluded, therefore, that only tetanic frequencies < 70 Hz might reliably be expected to show a sustained response after reversal of nondepolarizing block, and that the application of higher tetanic frequencies which do show fade in the normal state would introduce an undue cause for concern to the clinician. A reliable index of recovery from nondepolarizing neuromuscular block must be the test which correlates best with clinical criteria of recovery. In the present study, we have demonstrated that the T_4 response predicts that the single twitch at 0.15 Hz should have returned to control height and that tetanus at 50 Hz for 5 s should be sustained when the T_4 ratio exceeds 0.7. A T_4 ratio of 0.7 and higher correlates with clinical signs of adequate recovery from nondepolarizing neuromuscular block.[14–16]

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