

FACTORS AFFECTING TRAIN-OF-FOUR FADE

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The use of a train-of-four (TOF) pattern of stimulation (Ali, Utting and Gray, 1970) to detect and quantify neuromuscular blockade has become firmly established. It has been suggested that a relationship exists between the degree of single, or initial, twitch depression and the amount of TOF fade or number of responses within the train (Lee, 1975). However, more recently, the variability of this relationship with the same neuromuscular blocker during onset and spontaneous offset of neuromuscular blockade has been demonstrated (Bowman, 1980). In addition, Williams, Webb and Calvey (1980) have demonstrated that individual neuromuscular blocking drugs may be associated with varying degrees of train-of-four fade during the onset of neuromuscular blockade; these authors have speculated that this observation may be attributable to the action of such drugs at more than one site within the neuromuscular junction.

We have compared the pattern of TOF fade of two neuromuscular blocking drugs, atracurium and vecuronium, during both onset and spontaneous offset of neuromuscular blockade, and also studied the fade characteristics of varying doses of atracurium during onset of action.

PATIENTS AND METHODS

After ethics committee approval and with informed consent, we studied patients undergoing surgery requiring the use of neuromuscular blocking drugs. No patient of greater than 20% above ideal weight was included in the study. Neuromuscular monitoring was undertaken in a standard manner using the same recording equipment for all patients.

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SUMMARY

The characteristics of the train-of-four response during neuromuscular blockade with two agents, atracurium and vecuronium, have been compared. During onset of blockade, at 75% depression of the initial twitch, atracurium was associated with significantly more fade than was vecuronium, and larger doses of atracurium were associated with less fade than smaller doses of the same agent. In addition, with both agents, the degree of fade at a given amount of initial twitch depression was significantly less during onset than during spontaneous offset of action. The degree of train-of-four fade bears no fixed relationship to depression of the initial twitch.

Before induction of anaesthesia, the left arm of the subject was immobilized in a splint and a force displacement transducer (Grass FTO3C) was attached to the thumb. The force of contraction of adductor pollicis following ulnar nerve stimulation was recorded using a Devices pre-amplifier and two-channel chart recorder. The linearity of the recording system in the range 0.05–2.0 kg was confirmed by the use of weights. Stimulation of the ulnar nerve was by supramaximal 0.2-ms square wave impulses delivered in a train-of-four pattern at 2 Hz for 2 s via surface electrodes at the wrist, repeated at 12-s intervals (Myotest).

Two indices of neuromuscular blockade were recorded: the height of the first, or initial, response in the train (T1) compared with control T1 (T1:control) (%) and the ratio of the height of the fourth to the height of the first response in the same train (T4 ratio). Because of the 10-s interval between trains, the first response was considered to be an unmodified single twitch response.

The basic anaesthetic technique in all patients was as follows. Patients were unpremedicated. Anaesthesia was induced with 2.5% thiopentone injected via an indwelling needle on the dorsum of the right hand, in a dose approximately 20% greater than that required to abolish the eyelash reflex. After baseline neuromuscular recordings had been made, the neuromuscular blocking drug was injected via the same needle, preceded and flushed with saline 1 ml (time 0). The patients received nitrous oxide in oxygen (2:1) with 3% enflurane through a face mask and Bain type co-axial breathing system until intubation of the trachea at 3 min, at which time the inspired concentration of enflurane was reduced to 1% and continued at this value until completion of the recording.

In the first part of the study, either atracurium 0.25 mg kg⁻¹ or vecuronium 0.06 mg kg⁻¹ was randomly administered ($n = 10$ in each group). (Published data suggest that these doses of the two neuromuscular blocking drugs are approximately equipotent.) The T4 ratio of trains with T1:control values nearest to 75%, 50% and 25% were recorded during onset and spontaneous offset of neuromuscular blockade.

In the second part of the study, atracurium 0.25 mg kg⁻¹, 0.375 mg kg⁻¹ or 0.5 mg kg⁻¹, was randomly allocated ($n = 10$ each group). The T4 ratio of trains with T1:control values of 25% and the

time to achieve this T1:control value were recorded.

Statistical analysis was with Student's t test, paired or unpaired as applicable.

RESULTS

All results are expressed as mean (SD). The ages and weights of the groups in the first part of the study were not significantly different: atracurium, (A) 31.2(9.4) yr, 63.8(9.9) kg; vecuronium (V) 22.8 (10.1) yr, 62.1(10.1) kg ($n = 10$ each group).

The T4 ratios at T1:control values of 75%, 50% and 25% during onset and offset of blockade are compared in table I. During onset, the degree of fade at T1: control 25% was greater with atracurium than with vecuronium ($P < 0.05$). With both neuromuscular blockers, there was significantly more fade during offset than during onset at all three chosen values of T1:control ($P < 0.001$ all sets) (table II).

Variations in T4 ratio at T1:control 25% with different doses of atracurium are shown in table III. With atracurium 0.25 mg kg⁻¹, the mean (SD) T4 ratio was 0.26(0.06); with atracurium 0.375 mg kg⁻¹ it was 0.53(0.11); and with atracurium 0.5 mg kg⁻¹, 0.65(0.06). Thus the largest dose of atracurium was associated with significantly less fade than was either the middle ($P < 0.01$) or the smallest dose ($P < 0.001$).

TABLE I. Comparison between atracurium 0.25 mg kg⁻¹ and vecuronium 0.06 mg kg⁻¹, during both onset and offset of neuromuscular blockade. Mean (SD) T4 ratio at T1:control 75%, 50% and 25%.
*Degree of fade with atracurium significantly greater than with vecuronium ($P < 0.05$)

T1:control	Onset		Offset	
	A	V	A	V
75%	0.71 (0.08)	0.74 (0.06)	0.36 (0.14)	0.31 (0.09)
50%	0.50 (0.15)	0.62 (0.13)	0.19 (0.15)	0.16 (0.09)
25%	0.26 (0.17) *	0.44 (0.18)	0.06 (0.11)	0.02 (0.02)

TABLE II. The same data as in table I, arranged to show a comparison between onset and offset, for both atracurium 0.25 mg kg⁻¹ and vecuronium 0.06 mg kg⁻¹. The difference between mean (SD) T4 ratios during onset and offset at each T1:control value for both drugs is significant ($P < 0.001$)

T1:control	Atracurium		Vecuronium	
	Onset	Offset	Onset	Offset
75%	0.71 (0.08)	0.36 (0.14)	0.74 (0.06)	0.31 (0.09)
50%	0.50 (0.15)	0.19 (0.15)	0.62 (0.13)	0.16 (0.09)
25%	0.26 (0.17)	0.06 (0.11)	0.44 (0.18)	0.02 (0.02)

TABLE III. *Individual and mean (SD) T4 ratio at T1:control 25% with different doses of atracurium, during onset of blockade*

	Dose of atracurium		
	0.50 mg kg ⁻¹	0.375 mg kg ⁻¹	0.25 mg kg ⁻¹
	0.53	0.68	0.21
	0.60	0.60	0.26
	0.63	0.56	0.00
	0.73	0.50	0.25
	0.75	0.45	0.23
	0.67	0.46	0.28
	0.66	0.44	0.68
	0.65	0.52	0.25
	0.60	0.36	0.23
	0.63	0.70	0.23
Mean (SD)	0.65 (0.06)	0.53 (0.11)	0.26 (0.06)

DISCUSSION

The train-of-four mode of stimulation is commonly used in research and clinical practice to determine the degree of neuromuscular blockade. It is more sensitive than the single twitch response and as sensitive as a 50-Hz tetanus (Ali, Lebowitz and Ramsey, 1981). Observation of the number of responses within a train, or calculation of a train-of-four ratio will delineate the degree of blockade without reference to a control train-of-four response; the absolute force of contraction of the responses in a train, however, can only be compared with the patient's normal response if a control train-of-four has been obtained. Working with tubocurarine, Lee (1975) showed that the response to the fourth stimulus disappeared when the first response had been reduced to 20–25% of control, during onset of blockade. This correlation between initial, or single twitch, depression and train-of-four fade is often cited without reference to the drug and its concentration, or the phase of blockade (Miller and Savarese, 1981; Viby-Mogensen, 1982).

The results of the present study demonstrate that the train-of-four ratio and the depression of the single twitch bear no fixed relationship. The relationship varied between neuromuscular blocking agents and during onset and offset of blockade. Atracurium caused more fade than vecuronium during onset, and both drugs exhibited more fade during offset than during onset. Our results confirm the greater degree of fade during offset previously described with vecuronium (Bowman, 1980).

Single twitch depression and train-of-four fade

may be the results of neuromuscular blockers binding to different sites. Bowman (1980) suggested that fade may be an expression of prejunctional receptor binding, impairing transmitter mobilization during rapid stimulation. Another possibility is that the neuromuscular blocking drug plugs open sodium channels at, or near, prejunctional receptors. This will occur in a use-dependent fashion, being therefore more marked at high rates of stimulation (Standaert, 1982). The single twitch response appears to be more a function of postsynaptic binding. Certainly, the prejunctional receptors appear to be structurally disparate from the postjunctional receptors, and have more similarity with ganglionic cholinceptors. It is not surprising that different neuromuscular blocking drugs will have differing affinities for pre- and postjunctional binding sites and will therefore affect the train-of-four response in different, but characteristic, patterns. Atracurium causes more fade than vecuronium during onset at T1:control 25% and therefore has greater activity at fade "receptors", wherever these may be within the neuromuscular junction. No significant difference between the two agents was demonstrated at T1:control 75% and 50%; this may have been because the size of the study groups was too small to reveal a statistical significance of the small differences at these stages.

The rate of binding to the single twitch and fade "receptors" was different also. With both neuromuscular blockers there was more fade at each value of T1:control during offset than during onset, suggesting that the rate of binding or expression of binding occurs more slowly at fade "receptors". The

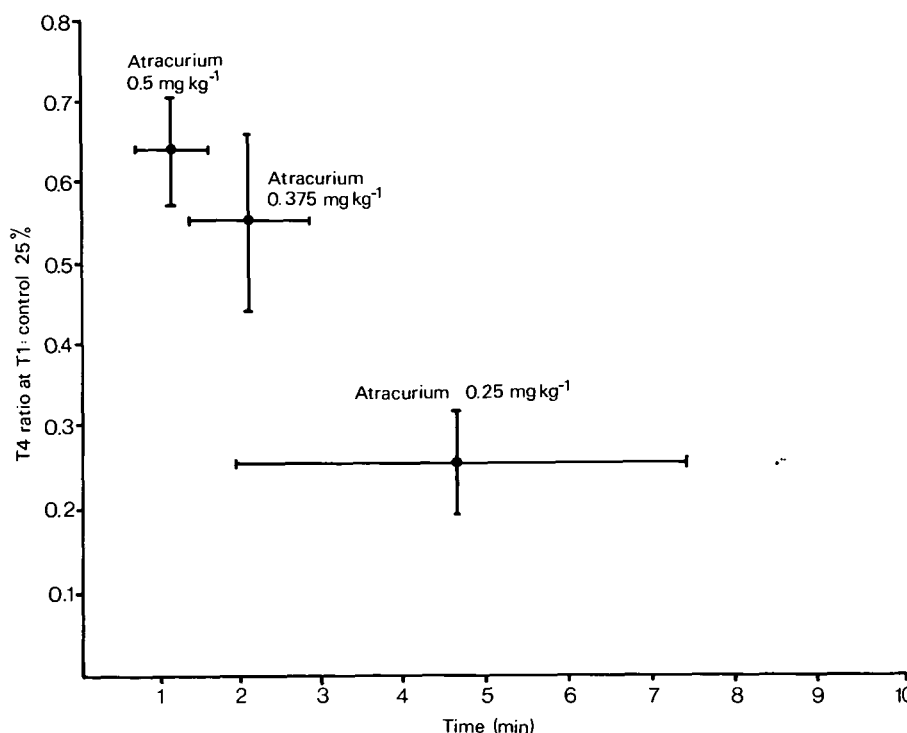


FIG. 1. Association between T4 ratio and T1:control 25% and the time taken to achieve this T1:control value (mean (SD)).

pharmacodynamics of neuromuscular blocking drugs at the neuromuscular junction are complex (Hull, 1982). Drug must diffuse through the bio-phase to reach the receptor. The rate of diffusion will be affected by blood concentration, and the disparity between activity at single twitch and fade "receptors" may be enhanced by varying the dose of drug. In this study, larger doses of atracurium were associated with less fade at T1:control 25% than were smaller doses, during onset of blockade. However, alterations in dose vary the time taken to achieve a certain degree of blockade, and it is not possible from this study to separate the effects of dose and of time on fade. Figure 1 shows, for the three doses of atracurium, the mean values of the association between the T4 ratio at T1:control 25% and the time to achieve this T1:control value, and also demonstrates the greater variability of onset times as the dose was reduced.

It should be noted that enflurane is known to potentiate the action of neuromuscular blocking agents and may itself have effects within the neuromuscular junction (Waud and Waud, 1975). However, it is unlikely that this volatile agent could

have exerted significant effects during the few minutes of onset of blockade in the present study. In addition, all patients were exposed to the same inspired concentration of enflurane throughout the study period, and Bowman (1980) has previously demonstrated a similar difference between onset and offset with vecuronium in the absence of enflurane.

The finding that the relationship between depression of the initial twitch and fade is not fixed is of importance. In clinical practice the magnitude of the train-of-four ratio is often used at the end of surgery to assess the degree of residual blockade and the requirement for pharmacological antagonism. A safe value is generally accepted to be of the order 0.5–0.75. However, it is really the absolute height (force of contraction) of the fourth and therefore subsequent twitch response which is important in determining sustained muscle power. With different neuromuscular blocking drugs, at an identical T4 ratio, the magnitudes of the first, and therefore the fourth, twitch responses will be different. This raises the possibility that different agents possess an individual "safe" T4 ratio which incorporates the fade characteristics of the agent, but since the T4

ratio may not accurately quantify the degree of blockade, comparisons between studies using this mode of stimulation may give rise to erroneous conclusions. Perhaps the fourth twitch:control fourth twitch (T4:control) value would have more clinical relevance.

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