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The Relation between the Response to "Train-of-four" Stimulation and Receptor Occlusion during Competitive Neuromuscular Block

B. E. Waud, M.D., and D. R. Waud, M.D.†*

The responses to a train of four indirect stimuli at 0.5-second intervals were examined in the cat and the dog during recovery from neuromuscular block produced by *d*-tubocurarine. The relation of the twitch responses during the train to the fractional receptor occlusion by the competitive neuromuscular blocking agent was measured. The response to the fourth stimulus in the train returns to normal when about 25–30 per cent of the receptors have become available. Thus, the train of four is slightly more sensitive to receptor occlusion than the single twitch, which returns when 20–25 per cent of the receptors are free. However, 50 per cent of the receptor pool must be available before fade in response to a 100/sec tetanic stimulus lasting 5 seconds returns to normal. Thus, the response to tetanic stimulation at 100/sec is a considerably more sensitive indicator of receptor block than either the twitch response or the fade in a train of four twitches. (Key words: Margin of safety; *d*-Tubocurarine; Train of four; Competitive neuromuscular block.)

THE MARGIN OF SAFETY of neuromuscular transmission is such that only 20–25 per cent of the postsynaptic receptors need be free for transmission to occur.[1, 2] Thus, the twitch response to a single stimulus applied to a motor nerve is a relatively insensitive index of whether receptors are blocked; 75–80 per cent can be occluded, yet the twitch can be normal. Clinically, the fade of an indirectly-elicited tetanus appeared to be a more sensitive indicator of receptor block,[3, 4] and direct measurement confirmed this; about 50 per cent of the receptor pool had to be free before the response to a 100/sec tetanic stimulus of 5 seconds' duration returned to its control value.[2]

Recently, it has been suggested that a brief train of twitches at a low frequency might also be a more sensitive indicator than a single twitch. Specifically, the ratio of height of the last twitch to height of the first twitch in a train of four responses 0.5 seconds apart has been proposed as an index of recovery.[5–7] The relation between this index and the percentage of receptors blocked has therefore been measured during recovery from neuromuscular block by *d*-tubocurarine.

Methods

The experimental preparation was identical to that used previously to calibrate the tetanic response as an index of recovery.[2] Measurements were made in the cat after administration of chloralose (80 mg/kg) and in the dog after administration of pentobarbital (35 mg/kg). The increase in dose of succinylcholine necessary to match a control level of extracellularly-recorded depolarization was used to estimate the fraction of receptors blocked by *d*-tubocurarine. In three cats, the mechanical response used was the isometric twitch of the tibialis anterior, stimulated through the sciatic nerve. Four experiments were done in the cat soleus muscle to compare behavior of red and white fibers. One preparation was made in a dog to see whether there was any evidence of appreciable variation between species.

The design of the experiment was as follows. After the muscle had been prepared, a series of control responses to single shocks, to a train of four stimuli at half-second intervals, and to tetanic stimulation at 100/sec for 5 seconds were obtained. A series of graded

* Assistant Professor of Anaesthesia.
† Associate Professor of Pharmacology.
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Address reprint requests to: Dr. B. E. Waud, Department of Anaesthesia, Peter Bent Brigham Hospital, 721 Huntington Avenue, Boston, Massachusetts 02115.

TABLE 1. Comparison of Indices of Recovery from Neuromuscular Block

Index	Per Cent of Receptors Needed for Normal Response*	Advantages/Disadvantages
Head lifting, hand grip, maximal inspiratory or expiratory force	?	Simple, utilizes tetanic response, which is more sensitive than a twitch response, needs conscious patient, but not painful, uncalibrated
Eye opening	?	As above, but in muscle characteristically thought to be sensitive to competitive block
Twitch response	20–25	Requires electronic stimulator, uncomfortable, sensitivity low but known; often, it's hard to remember how big the control response was
Train-of-four ratio	25–30	Requires more complex stimulator, uncomfortable but less so than tetanus; sensitivity slightly better than twitch; does not need conscious patient, and not too uncomfortable for patient partly recovered from anesthesia; comparison made within a given train so precise value of control response less crucial than with single twitch
Tetanic-fade ratio		
30/sec	20–25	No more sensitive than single twitch but more uncomfortable
100/sec	50	More sensitive than single twitch or train of four, but much more painful (a distinct disadvantage since characteristically patient may be conscious when measurement is needed)
200/sec	70	Most sensitive of all responses to nerve stimulation, but painful

* The more receptors needed, the more sensitive the index.

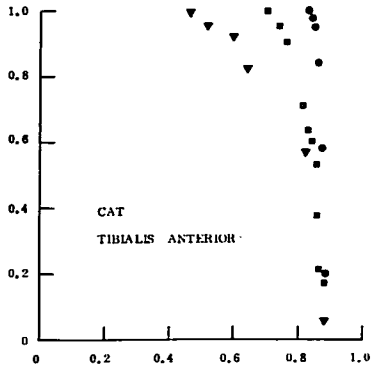
doses of succinylcholine was given intra-arterially, and the endplate depolarizations produced were recorded to give a control dose–response curve. Then sufficient *d*-tubocurarine was given to produce profound neuromuscular block (about 0.2–0.3 mg/kg, iv). The rest of the experiment consisted of following recovery of the twitch response, the tetanic response, and the response to a train of four stimuli. (Frequent tetanic responses were avoided early in recovery to minimize the chance of distorting results by posttetanic facilitation.) Also during recovery, sensitivity to the depolarizing action of succinylcholine was tested to obtain a measure of the fraction of receptors still blocked (the details of the calculations are available in references 1 and 8). Thus, series of mechanical responses (twitch, tetanic, or train-of-four) corresponding to various degrees of receptor block were obtained.

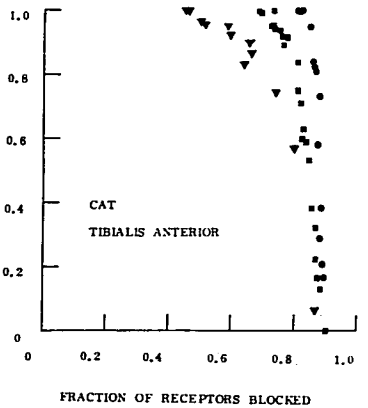
FIG. 1 (*top, left*). Comparison of single twitches, train-of-four responses, and tetanic fade at 100/sec. Cat tibialis anterior. *Ordinate:* mechanical response (see Text). *Abscissa:* fractional receptor occlusion by *d*-tubocurarine. The train-of-four response is slightly more sensitive than the single twitch to block by *d*-tubocurarine, but the tetanic response is considerably more sensitive than either.

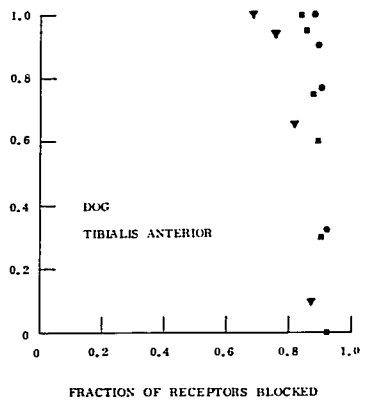
FIG. 2 (*top, right*). Comparison of single twitches, train-of-four responses, and tetanic fade at 100/sec. Pooled results of three experiments like that of figure 1.

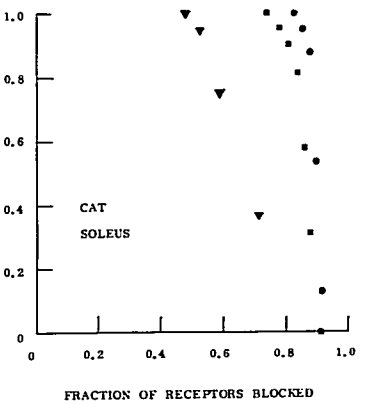
FIG. 3 (*bottom, left*). Comparison of single twitches, train-of-four responses, and tetanic fade at 100/sec in the tibialis anterior of a dog. Plot as in figure 1. The dog behaves like the cat.

FIG. 4 (*bottom, right*). Comparison of single twitches, train-of-four responses, and tetanic fade at 100/sec in the soleus of a cat. Plot as in figure 1. The soleus behaves like the tibialis anterior.









TWITCH HEIGHT AS FRACTION OF NORMAL ●

RATIO OF FOURTH TO FIRST TWITCH IN A TRAIN OF FOUR ■

TETANIC FADE RATIO ▼

These results are summarized by plotting, for example, the degree of tetanic fade ("tetanic-fade ratio") against the corresponding fraction of receptors blocked.

The *d*-tubocurarine and succinylcholine were the chloride and iodide, respectively. Both were obtained from K and K Laboratories.

Results

Cat Tibialis Anterior

The results of a representative experiment are given in figure 1; the results of three such preparations are pooled in figure 2. In both, the mechanical responses to nerve stimulation are plotted as ordinates. The twitch responses are plotted as fractions of control responses. For the trains of four responses, the ratios of the heights of the last to those of the first responses are plotted. For the tetani, the fade ratio—the ratio of the final to the peak tension—is plotted relative to the control value. The abscissae are the fractions of receptors occupied by *d*-tubocurarine.

Start at the lower right-hand corner, where all the receptors are occupied by *d*-tubocurarine and no mechanical response is seen. As receptor occlusion by *d*-tubocurarine diminishes, and about 10 per cent of the receptors become free, the twitch response (circles) begins to recover, and it returns to normal when about 20–25 per cent of the receptors have become available. This agrees with the previous measurements.[1, 2] The values obtained with trains of four responses (squares) lie slightly to the left. About 25–30 per cent of the receptors are necessary before this index returns to normal. In contrast, the fade in response to 100/sec tetanic stimulation (triangles) does not return to normal until about 50 per cent of the receptors have become available (again in agreement with previous results[2]).

Dog Tibialis Anterior

The results obtained in a dog are shown in figure 3. Again, the values with the train of four index lie between those for single twitches and those for 100/sec tetanic stimulation, but much closer to the former.

Cat Soleus

The results from a representative preparation are summarized in figure 4. This muscle behaves like the tibialis anterior.

Discussion

As might be expected, the response to a brief train of stimuli is a slightly more sensitive index of block of receptors by a competitive neuromuscular blocking agent than is the response to a single twitch, but the fade in response to a 5-second tetanic stimulus at 100/sec is much more sensitive than either. Since the two species examined behave similarly, it is reasonable to expect that human muscle would not differ.

Thus, the advantages of the train-of-four index must lie not so much in sensitivity but in other features. For example, the train of four stimuli produces less discomfort than a 100/sec tetanic stimulus, and the use of this index does not require knowledge of the control value. Table 1 compares various indices of recovery from neuromuscular block.

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