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Dose–Response Relationships for Edrophonium and Neostigmine as Antagonists of Atracurium and Vecuronium Neuromuscular Blockade

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To determine the potencies of edrophonium and neostigmine as antagonists of nondepolarizing neuromuscular blockade produced by atracurium and vecuronium, dose–response curves were constructed for both antagonists when given at 10% spontaneous recovery of first twitch height. Ninety ASA physical status 1 and 2 adults were given either 0.4 mg/kg atracurium or 0.08 mg/kg vecuronium during thiopental–nitrous oxide–enflurane anesthesia. Train-of-four stimulation was applied to the ulnar nerve every 12 s, and the force of contraction of the adductor pollicis muscle was recorded. When spontaneous recovery of first twitch height reached 10% of its initial control value, edrophonium (0.1, 0.2, 0.4, or 1 mg/kg) or neostigmine (0.005, 0.01, 0.02, or 0.05 mg/kg) was administered by random allocation. Neuromuscular function in another ten subjects was allowed to recover spontaneously. Assisted recovery was defined as actual recovery minus mean spontaneous recovery observed in patients who were not given antagonists. First twitch recovery was initially more rapid when vecuronium was antagonized compared with atracurium, but no difference was detected after 10 min. At 10 min the neostigmine ED_{80} was 0.022 ± 0.003 (SEM) mg/kg after atracurium and 0.024 ± 0.003 mg/kg after vecuronium. The edrophonium ED_{80} was 0.44 ± 0.11 mg/kg with atracurium and 0.46 ± 0.12 mg/kg with vecuronium, giving a neostigmine:edrophonium potency ratio of 20. Atracurium train-of-four fade could be antagonized more easily with edrophonium, whereas that of vecuronium was more easily antagonized by neostigmine. It is concluded that edrophonium and neostigmine are not equally effective against atracurium and vecuronium. (Key words: Antagonists, neuromuscular relaxants: edrophonium; neostigmine. Monitoring: train-of-four. Neuromuscular relaxants: atracurium; vecuronium.)

EDROPHONIUM and neostigmine are commonly used to antagonize the effects of nondepolarizing neuromuscular relaxants. These drugs have different onsets of action[1,2] and may also have different mechanisms of action.[3–6] Recovery from neuromuscular blockade might depend on several factors, including twitch height when the antagonist is given,[7–9] rate of spontaneous recovery, type of relaxant given,[10,11] and dose of antagonist.[2,10,12]

Any comparison between edrophonium and neostigmine may be misleading if only one dose of each agent is administered. Therefore, it is important to determine dose–response relationships for these agents. These have been obtained during constant infusions of *d*-tubocurarine (*d*Tc),[2,7] pancuronium,[13] or vecuronium.[13] Infusions were used to separate the effect produced by the antagonist from the spontaneous recovery of the relaxant. However, when antagonists are used in clinical practice, spontaneous recovery occurs at the same time antagonist-assisted recovery takes place. After a bolus dose of a long acting relaxant such as pancuronium or *d*Tc, the potencies of neostigmine or edrophonium appear similar to those obtained during a constant infusion of the relaxant, probably because of the slow elimination of the relaxant.[10] This may not be the case with atracurium and vecuronium, which have rapid rates of spontaneous recovery that in turn may enhance assisted recovery.

Studies with long acting relaxants have shown that the effectiveness of the antagonist agent also depends on which muscle relaxant has been used.[10,11] The same could be true of atracurium and vecuronium. The variable used to measure the response is also important. For example, when used to antagonize pancuronium, neostigmine is 12 times as potent as edrophonium if first twitch is considered but 25 times as potent if train-of-four ratio is measured.

Although many workers have studied the effect of edrophonium or neostigmine in patients who had received atracurium or vecuronium,[6–8,14–16] no dose–response relationships were obtained during spontaneous recovery of the relaxant because only one or two doses were used. Furthermore, possible differences between the antagonism of atracurium- *versus* vecuronium-induced blockade have not been investigated. Finally, potency estimates for edrophonium and neostigmine have not been obtained with simultaneous measurement of first twitch height and train-of-four ratio. Therefore, this study was designed to determine dose–response relationships for neostigmine and edrophonium as antagonists of atracurium and vecuronium blockade. To eliminate the confounding effect of twitch height at the time the antagonist is administered, the antagonist was given at the same degree of spontaneous recovery.

Materials and Methods

The protocol was approved by the Hospital Ethics Committee. After informed consent was obtained, 90 patients, ASA physical status 1 or 2, were studied during

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TABLE 1. Patient Demographic Data

Relaxant	N	Sex (M/F)	Age (mean ± SEM) (yr)	Weight (mean ± SEM) (kg)
Atracurium	45	16/29	51 ± 2	65 ± 2
Vecuronium	45	15/30	49 ± 2	65 ± 2

various elective surgical procedures. Patients with hepatic, renal, or neuromuscular disease were excluded, as were those with electrolyte abnormality and those taking any medication known or suspected to interfere with neuromuscular function.

Atropine, 0.006–0.01 mg/kg, or glycopyrrolate, 0.003–0.005 mg/kg, and morphine, 0.1 mg/kg, or meperidine, 1 mg/kg, were given intramuscularly 1 h before the scheduled start of the surgical procedure. On arrival in the operating room, ECG and a noninvasive arterial blood pressure monitor were applied. Anesthesia was induced with thiopental, 3–5 mg/kg, and maintained with N_2O 70%, and enflurane, in O_2. The ulnar nerve was stimulated supramaximally at the elbow with square pulses of 0.2 ms duration, delivered at a frequency of 2 Hz for 2 s (train-of-four) and repeated every 12 s. The hand and forearm were immobilized in a splint, and the force of contraction of the adductor pollicis muscle was measured with a force–displacement transducer (Grass FT-10) and recorded on paper. After establishment of a stable neuromuscular response, the patients received either 0.4 mg/kg atracurium, or 0.08 mg/kg vecuronium. Tracheal intubation was performed when neuromuscular response was abolished, and the patient's lungs were ventilated using a Mapleson D circuit with a fresh gas flow of 70 $ml \cdot kg^{-1} \cdot min^{-1}$. After tracheal intubation the inspired enflurane concentration was maintained at 0.5–1.0%.

When first twitch height had recovered to 10% of the control value, the patients received either edrophonium, 0.1, 0.2, 0.4, or 1 mg/kg, neostigmine, 0.005, 0.01, 0.02, or 0.05 mg/kg, or no antagonist drug. The selection was made by random allocation. Each dose of each antagonist agent was given to ten patients, five of whom had received atracurium and five who received vecuronium. Atropine, 0.3–1.5 mg, was administered when appropriate. No other antagonist was given for at least 10 min and the inspired enflurane concentration was not altered. At the end of the surgical procedure, an additional dose of antagonist was given if the train-of-four ratio was less than 0.7 or if the patients had clinical signs of inadequate neuromuscular function.

Every minute after administration of the antagonist the height of the first twitch (T1) was measured and expressed as a percentage of initial control. Train-of-four ratio (T4/T1) was also obtained. Then, the degree of assisted recovery, defined as the actual recovery minus the spontaneous recovery that would have taken place in the absence of antagonist, was calculated. This was done by subtracting from the actual recovery the mean spontaneous recovery observed in patients who did not receive any antagonist agent. The result was expressed as a percentage of the maximum possible assisted recovery, which is equal to 100% minus mean spontaneous recovery. These calculations were made for T1 and T4/T1.

Dose–response relationships were calculated for T1 and T4/T1 by linear regression of the logit transformation of assisted recovery on the logarithm of the dose. From these, the doses of antagonist expected to produce 50% and 80% recovery (ED_{50} and ED_{80}) were obtained every minute for 10 min after the administration of the drug. The SE of estimate for the mean was used as an index of dispersion.[17] Comparisons were made between the potencies of the antagonist drugs when used against each relaxant and between the ability of the relaxants to be antagonized. Statistical analyses were made using analysis of variance for repeated measures and the Newman-Keuls method.[18] The results were considered statistically significant when the P value was less than 0.05. To examine the variability in the response of edrophonium and neostigmine, the SE associated with each drug were compared, assuming a normal distribution and using Student's t test.[19]

Results

The patients' demographic data are shown in table 1. The subjects in the atracurium and vecuronium groups were comparable with respect to age, sex, and weight. The duration of action, defined as the interval between the administration of the relaxant and recovery to 10% first twitch height, was 33.1 ± 1.1 min for vecuronium and 37.9 ± 1.1 min for atracurium ($P < 0.05$).

In the absence of antagonist, the spontaneous recovery for the first 10 min following return to 10% first twitch height proceeded at similar rates with both relaxants (figs. 1 and 2). Mean first twitch height reached 37.6% ± 2.6% and 40.6% ± 4.6% with atracurium and vecuronium, respectively (NS). Corresponding train-of-four ratios were 19.0% ± 3.5% and 11.0% ± 4.9%, respectively (NS).

Figures 1 and 2 show first twitch height as a function of time after administration of the antagonist. For the majority of the doses used in this study, recovery was initially more rapid if the relaxant was vecuronium. However, no differences were noted at 10 min.

The dose–response relationships for assisted recovery were calculated for each minute after the administration of the antagonist. These are shown for 5 and 10 min in figures 3 and 4. For each relaxant-antagonist pair, the curves were shifted to the left between 5 and 10 min, indicating a more complete antagonism with time. The

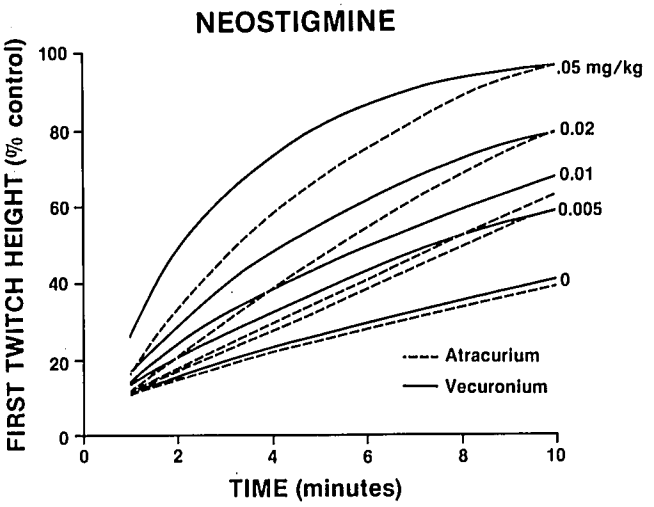

FIG. 1. Mean first twitch height *versus* time after administration of various doses of neostigmine. Antagonism of neuromuscular blockade was attempted when first twitch height reached 10% of its control value. The relaxants used were either atracurium or vecuronium. Standard errors were omitted for the sake of clarity.

slopes of the curves obtained with edrophonium were usually flatter than the corresponding curves for neostigmine. The curve describing train-of-four ratio against dose after vecuronium paralysis was significantly flatter ($P < 0.05$) with edrophonium than neostigmine.

The ED_{50} and ED_{80} values for neostigmine and edrophonium were derived from the dose–response curves, such as those illustrated in figures 3 and 4. These ED values are expressed as a function of time after administration of the antagonist in figures 5 and 6. Up to and

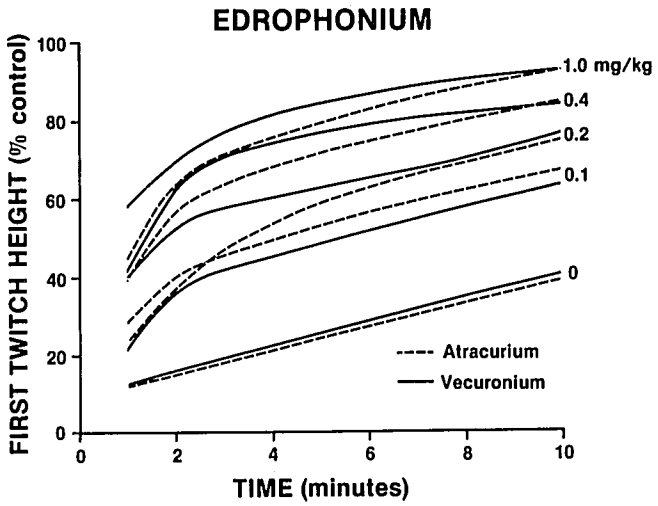

FIG. 2. Mean first twitch height *versus* time after administration of various doses of edrophonium. Antagonism of neuromuscular blockade was attempted when first twitch height reached 10% of its control value. The relaxants used were either atracurium or vecuronium. Standard errors were omitted for the sake of clarity.

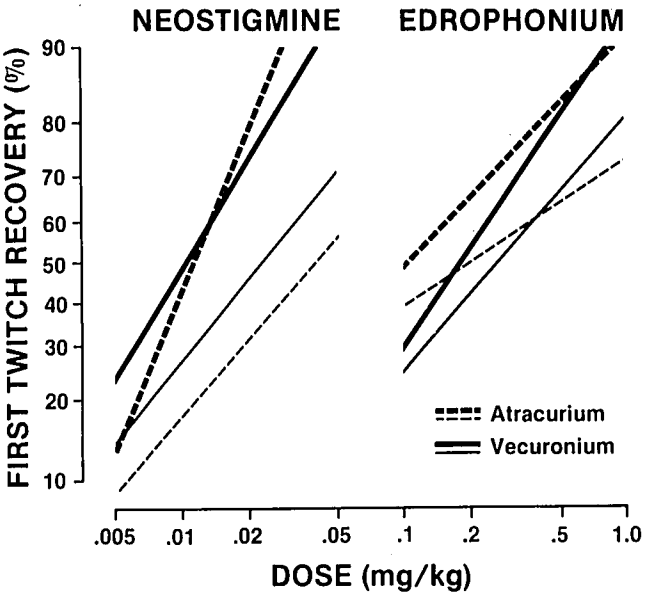

FIG. 3. Dose–response relationships of first twitch assisted recovery evaluated either 5 min (thin lines) or 10 min (thick lines) after administration of the antagonist as a function of the dose of neostigmine or edrophonium.

including 6 min after injection of the antagonist, the ED_{50} and ED_{80} for neostigmine were significantly less with vecuronium than atracurium ($P < 0.05$). However, there was no difference after 10 min (table 2). With edrophonium no statistically significant difference was detected between the two relaxants used (fig. 6 and table 2). The

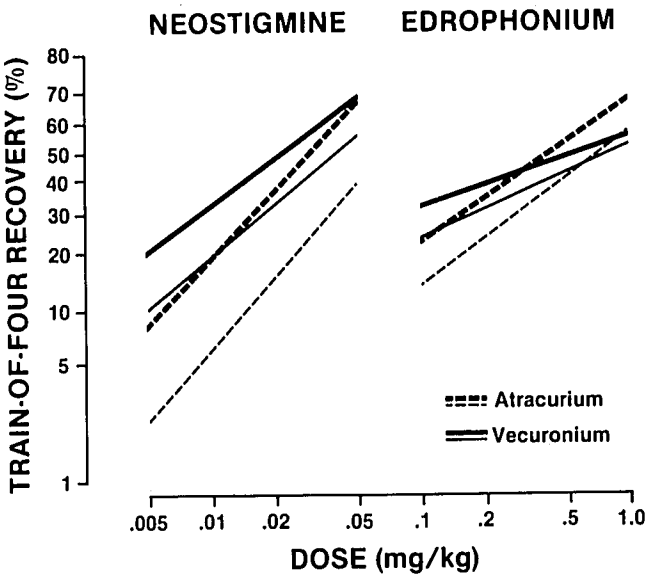

FIG. 4. Dose–response relationships of train-of-four assisted recovery evaluated either 5 min (thin lines) or 10 min (thick lines) after administration of the antagonist as a function of the dose of neostigmine or edrophonium.

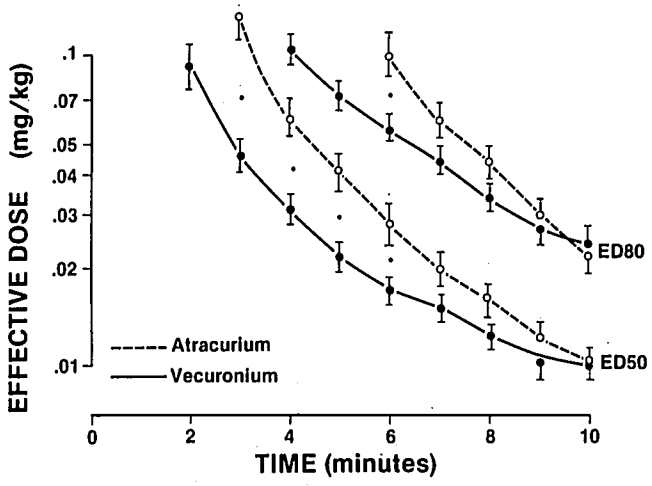

FIG. 5. Effective doses for 50% and 80% recovery (ED_{50} and ED_{80}) for neostigmine *versus* time after its administration for two relaxants. The error bars represent SE of the estimate for the mean. *Statistically significant difference, $P < 0.05$.

results for the train-of-four relationships are shown in table 3 and figure 7. The ED_{80} is not reported because it fell outside the range of doses tested. The neostigmine ED_{50} was significantly lower when used to antagonize vecuronium compared with atracurium for the first 7 min after injection ($P < 0.05$). For edrophonium there was no difference in the ED_{50} according to the relaxant used.

There was more variability associated with edrophonium than neostigmine. For example, the SE for neostigmine ED_{50} and ED_{80} obtained for T1 was 10% of the mean value, whereas it was 27% for edrophonium ($P < 0.02$) (table 2). With train-of-four responses, the SE for

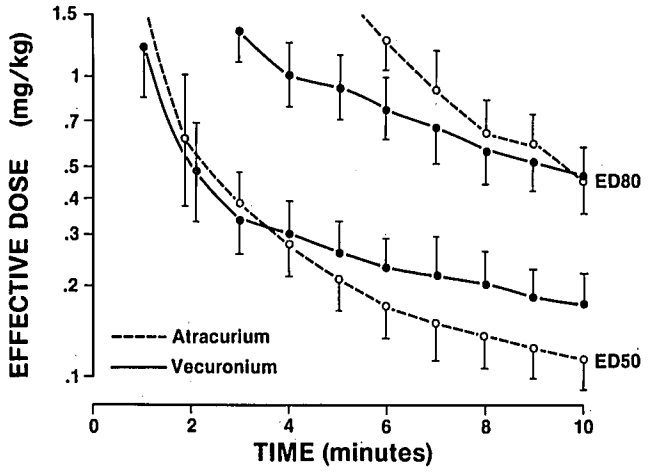

FIG. 6. Effective doses for 50% and 80% recovery (ED_{50} and ED_{80}) for edrophonium *versus* time after its administration for two relaxants. The error bars represent SE of the estimate for the mean. *Statistically significant difference, $P < 0.05$.

TABLE 2. Dose of Neostigmine or Edrophonium Required (mg/kg) for 50% (ED_{50}) and 80% (ED_{80}) Recovery of First Twitch Height 10 min after Injection of the Antagonist

	Atracurium	Vecuronium
Neostigmine		
ED_{50}	0.010 ± 0.001	0.010 ± 0.001
ED_{80}	0.022 ± 0.002	0.024 ± 0.002
Edrophonium		
ED_{50}	0.11 ± 0.03	0.18 ± 0.05
ED_{80}	0.44 ± 0.11	0.46 ± 0.13

Values are mean ± SE of estimate for the mean.

neostigmine was 10% of the mean with atracurium and 13% with vecuronium. However, with edrophonium these values were 19% and 28%, respectively, and the variability was statistically greater ($P < 0.05$) after vecuronium than atracurium (table 3).

The potency of neostigmine, expressed as a multiple of that of edrophonium, or potency ratio, was calculated at 80% twitch recovery (ED_{80}) and at 50% train-of-four recovery (ED_{50}). For first twitch ED_{80}, the potency ratio increased after time of administration of the antagonist. At 10 min neostigmine was 20.0 ± 4.2 times as potent as edrophonium after atracurium paralysis. After vecuronium the ratio was 19.2 ± 4.0 (NS). However, for train-of-four recovery, the potency ratio was greater if vecuronium had been used. At 10 min neostigmine was 26.1 ± 6.2 times as potent as edrophonium after vecuronium blockade, but only 14.8 ± 3.3 times as potent after atracurium ($P < 0.05$) (fig. 7).

The dose–response curves were used to estimate the effects of neostigmine, 0.02 and 0.04 mg/kg, and edrophonium, 0.5 and 1.0 mg/kg (table 4). Neostigmine was more effective at 5 min with vecuronium, and edrophonium produced greater recovery at 10 min with atracurium.

Discussion

The results from this study demonstrate that neostigmine- or edrophonium-assisted antagonism of vecuronium neuromuscular blockade is not identical to that of atracurium, a relaxant with comparable duration of action and recovery index. The effect of neostigmine, and to a

TABLE 3. Dose of Neostigmine or Edrophonium Required (mg/kg) for 50% Train-of-four Recovery 10 min after Injection of the Antagonist

	Atracurium	Vecuronium
Neostigmine ED_{50}	0.031 ± 0.003	0.023 ± 0.003
Edrophonium ED_{50}	0.46 ± 0.10	0.60 ± 0.17

Values are mean ± SE of estimate for the mean.

lesser extent edrophonium, on first twitch height was initially more rapid if the relaxant used was vecuronium. When the effect on train-of-four ratio was examined, edrophonium appeared relatively more potent after atracurium than after vecuronium blockade.

These results can be compared with those obtained previously under similar conditions with the longer acting agents pancuronium and *d*Tc.[10] Neostigmine appeared more potent with the shorter acting drugs. For example, 10 min after the administration of neostigmine, the ED_{80} for first twitch height was 0.022 ± 0.03 mg/kg with atracurium and 0.024 ± 0.03 mg/kg with vecuronium, compared with 0.045 ± 0.0055 mg/kg with pancuronium and 0.045 ± 0.0034 mg/kg with *d*Tc. For edrophonium the ED_{80} was 0.44 ± 0.11 mg/kg for atracurium and 0.46 ± 0.11 mg/kg for vecuronium, compared with 0.68 ± 0.10 mg/kg for pancuronium and 0.88 ± 0.09 mg/kg for *d*Tc.[10] In both studies the calculation of twitch height recovery takes into consideration the degree of spontaneous recovery that would be expected to take place in the absence of the antagonist agent. Thus, the discrepancy between long and intermediate acting relaxants would appear even greater if only total (spontaneous plus assisted) recovery had been considered. For example, 0.04 mg/kg neostigmine is expected to produce a T1 of 95%, 99%, 77%, and 76% after 10 min if given after atracurium, vecuronium, pancuronium, and *d*Tc, respectively. With 0.5 mg/kg edrophonium the T1 values would be 89%, 86%, 79%, and 68%, respectively. The increased potency of both antagonists against atracurium and vecuronium indicates that a rapid spontaneous recovery improves total recovery in two ways. First, a significant decrease in relaxant concentrations at the active site occurs with time. This implies that fewer receptors are occupied by the relaxant drug. In addition, antagonist drugs are much more efficacious when the intensity of the block is less.[7-9] It follows that the degree of assisted recovery improves with time. As a result, if a short acting relaxant has been given, total recovery is greater than with long acting relaxants because both spontaneous and assisted recovery are improved.

The results obtained with the train-of-four ratio are qualitatively similar. In this case the neostigmine ED_{50} was 0.031 ± 0.005 mg/kg with atracurium, 0.023 ± 0.003 with vecuronium, 0.031 ± 0.004 with pancuronium, and 0.043 ± 0.006 with *d*Tc.[10] The edrophonium ED_{50} was 0.46 ± 0.09 mg/kg, 0.60 ± 0.19 mg/kg, 0.77 ± 0.11 mg/kg, and 1.23 ± 0.16 mg/kg for the same relaxant drugs, respectively.[10] The effect of 0.04 mg/kg neostigmine on T4/T1 is expected to be 67%, 67%, 60%, and 49% with atracurium, vecuronium, pancuronium, and *d*Tc, respectively. With 0.5 mg/kg edrophonium the corresponding values would be 61%, 53%, 30%, and 32%, respectively. Although the ED_{50} usually increased with increasing duration of action of the relaxant drug, some observations suggest that other factors might be important. For example, neostigmine was more effective in reversing a train-of-four response previously depressed by vecuronium than atracurium. However, edrophonium was equally effective against the two relaxants. This suggests different properties of the relaxants and their antagonists.[3,4]

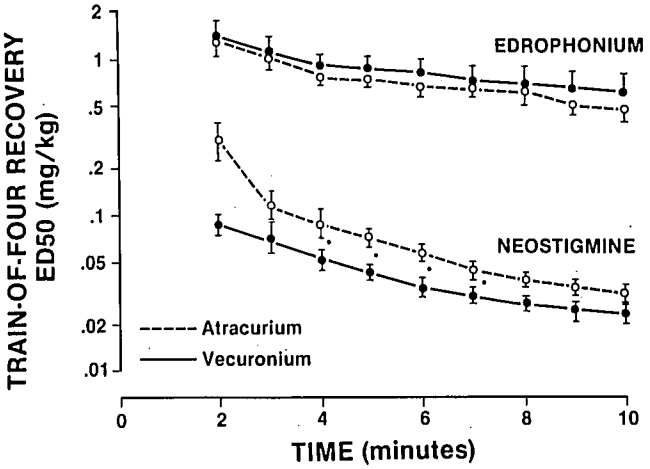

FIG. 7. Effective dose for 50% recovery of train-of-four ratio for edrophonium (top) and neostigmine (bottom) *versus* time after its administration for two relaxants. The error bars represent the SE of the estimate for the mean. *Statistically significant difference, $P < 0.05$.

TABLE 4. Effect on T1 and T4/T1 of 2 Doses of Neostigmine and Edrophonium 5 and 10 min after Injection

	Neostigmine		Edrophonium	
	0.02 mg/kg	0.04 mg/kg	0.5 mg/kg	1.0 mg/kg
Effect on T1 (% of control ± SE of estimate)				
Atracurium				
5 min	46 ± 3	60 ± 3	71 ± 3	79 ± 2
10 min	85 ± 2	95 ± 1	89 ± 2	94 ± 1
Vecuronium				
5 min	59 ± 2*	74 ± 2*	72 ± 5	81 ± 4
10 min	85 ± 2	99 ± 1*	86 ± 3	93 ± 2
Effect on T4/T1 (% ± SE of estimate)				
Atracurium				
5 min	18 ± 2	43 ± 6	43 ± 3	58 ± 3
10 min	47 ± 3	67 ± 5	61 ± 3	72 ± 2
Vecuronium				
5 min	34 ± 3*	52 ± 3	46 ± 3	55 ± 2
10 min	52 ± 3	67 ± 3	53 ± 3	60 ± 2*

* Statistically different from atracurium, $P < 0.01$.

This study supported a previous finding[6] that the effect of edrophonium was associated with more variability than that of neostigmine. The only exception was the train-of-four response after atracurium blockade when the properties of the two drugs might be particularly well matched. The reasons for this increased variability are unclear, but it appears unlikely that two drugs with the same mechanism of action would exhibit different degrees of variation. Different presynaptic *versus* postsynaptic activity between edrophonium and neostigmine is a possibility.[3] Other factors might also play a role. Unfortunately, a clinical study cannot resolve these questions.

The difference observed between the time courses of assisted recovery between atracurium and vecuronium cannot be explained by a different rate of spontaneous recovery. This finding suggests that atracurium and vecuronium have slightly different properties. The results of the present study support those of Caldwell *et al.*[15] who found that neostigmine tended to produce a more rapid antagonism of vecuronium induced neuromuscular blockade, whereas edrophonium seemed to be more effective following atracurium. Jones *et al.*[16] also reported shorter recovery times for neostigmine-assisted recovery when the relaxant used was vecuronium.

The potency ratio was found to vary with time after the injection of the antagonist. The lower neostigmine: edrophonium potency ratios shortly after their administration reflect the short onset of action of edrophonium relative to neostigmine. After 10 min the potency ratio for first twitch height was approximately 20 for both relaxants used. It was greater than the ratio of 12 determined with constant infusions of *d*Tc.[2] When the antagonists were tested during spontaneous recovery from blockade produced by long acting relaxants, the potency ratio was found to be approximately 12 for pancuronium and 16 for *d*Tc 10 min after injection of the antagonist.[10] Thus, the neostigmine:edrophonium potency ratio seems to depend on the relaxant used. For atracurium and vecuronium, the potency ratio appears to be greater than for pancuronium and *d*Tc. This might explain the relatively poorer recovery observed with edrophonium when a dose ratio of 12 was used.[6]

The potency ratio is also a function of which variable is measured. In this study potency ratio estimates based on train-of-four response were 14 after atracurium blockade *versus* 26 after vecuronium. The variability in the response was also much less with atracurium. It follows that edrophonium is more predictable in reversing the train-of-four fade produced by atracurium. In this respect, edrophonium appears to behave differently with atracurium compared with vecuronium (potency ratio of 28), pancuronium (potency ratio of 25),[10] or *d*Tc (potency ratio of 28).[10] These results support the hypothesis that first twitch height and train-of-four depression depend on different mechanisms of action and that antagonists might have different abilities against each of these mechanisms.

When neuromuscular blockade is antagonized, two variables need to be considered: the dose of the antagonist and the time interval until neuromuscular function has recovered completely. When comparing atracurium and vecuronium with longer acting relaxants, two strategies are possible with respect to antagonism of blockade: one could expect the same result in the same time with a lower dose of antagonist, or, alternatively, one could achieve a better recovery with the same dose of antagonist in the same time. The latter appears preferable, at least when antagonizing 90% blockade, because recovery following long acting relaxants antagonized by 0.04–0.05 mg/kg neostigmine or 0.5–1.0 mg/kg edrophonium takes a long time.[20] After 10 min recovery is much more complete if atracurium or vecuronium have been used. Thus, the present study involving intermediate acting nondepolarizing relaxants and previous work conducted on long acting relaxants[10] explain why the administration of pancuronium is associated with an unacceptably high incidence of postoperative residual paralysis[21] and impaired respiratory function.[22] These problems are largely avoided with atracurium[21,22] or vecuronium.[21] Thus, it seems preferable to try to obtain complete recovery instead of decreasing the dose of antagonist. In the clinical setting, at least in the presence of moderate to deep blockade, it appears prudent to administer relatively high doses of neostigmine (up to 0.05 mg/kg) or edrophonium (up to 1.0 mg/kg) when atracurium or vecuronium have been given.

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