General Anesthesia

Edrophonium effectively antagonizes neuromuscular block at the laryngeal adductors induced by rapacuronium, rocuronium and cisatracurium, but not mivacurium

[L'édrophonium antagonise efficacement le blocage neuromusculaire des adducteurs laryngés induit par le rapacuronium, le rocuronium et le cisatracurium, mais non par le mivacurium]

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Purpose: To examine the efficacy of antagonism of rapacuronium-, mivacurium-, rocuronium- and cisatracurium-induced neuromuscular block at the laryngeal adductors (LA).

Methods: One hundred four patients were randomly assigned to one of eight study groups. They either received rapacuronium 1.5 mg·kg⁻¹, mivacurium 0.25 mg·kg⁻¹, rocuronium 0.9 mg·kg⁻¹ or cisatracurium 0.15 mg·kg⁻¹. Patients in each treatment group either received edrophonium (0.5 mg·kg⁻¹) at 10% recovery of the first twitch (T1) of train-of-four (TOF) at the LA or were allowed to recover spontaneously from neuromuscular block. The effect of antagonism on speed of recovery of neuromuscular function at the LA was evaluated.

Results: The time to recovery to a TOF ratio of 0.9 at the LA, when compared to the spontaneous recovery group, was significantly shortened by the administration of edrophonium in patients receiving rapacuronium [19.2 ± 7.8 vs 26.2 ± 4.9 (mean $\pm$ SD) min], rocuronium (24.7 ± 14.3 vs 44.4 ± 13.0 min) and cisatracurium (24.2 ± 5.7 vs 35.1 ± 7.6 min). Edrophonium administration did not shorten complete recovery from mivacurium-induced block (15.7 ± 8.0 vs 17.6 ± 6.1 min).

Conclusion: Recovery from rapacuronium-, rocuronium- or cisatracurium- induced neuromuscular block to a TOF ratio of 0.9 as measured at the LA was shortened by the administration of edrophonium, when compared to spontaneous recovery.

Objectif: Vérifier l'efficacité antagoniste du blocage neuromusculaire des adducteurs laryngés (AL) induit par le rapacuronium, le mivacurium, le rocuronium et le cisatracurium.

Méthode : Cent quatre patients ont été répartis au hasard en huit groupes. Ils ont reçu, soit 1,5 mg·kg⁻¹ de rapacuronium, 0,25 mg·kg⁻¹ de mivacurium, 0,9 mg·kg⁻¹ de rocuronium ou 0,15 mg·kg⁻¹ de cisatracurium. Les patients de chaque groupe expérimental ont reçu de l'édrophonium (0,5 mg·kg⁻¹) à 10 % de récupération de la première stimulation (T1) d'un train-de-quatre (TDQ) aux AL, ou ont pu récupérer spontanément du blocage neuromusculaire. L'effet de l'antagonisme sur la vitesse de récupération de la fonction neuromusculaire des AL a été évalué.

Résultats : Le temps de récupération à un ratio de 0,9 d'un TDQ au niveau des AL, comparé au temps de récupération spontanée, a été significativement plus court avec l'administration d'édrophonium chez les patients qui ont reçu le rapacuronium [$19,2 \pm 7,8$ vs $26,2 \pm 4,9$ (moyenne $\pm$ écart type) min], le rocuronium ($24,7 \pm 14,3$ vs $44,4 \pm 13,0$ min) et le cisatracurium ($24,2 \pm 5,7$ vs $35,1 \pm 7,6$ min). L'administration d'édrophonium n'a pas raccourci le temps de récupération complète d'un bloc induit par le mivacurium ($15,7 \pm 8,0$ vs $17,6 \pm 6,1$ min).

Conclusion : La récupération d'un blocage neuromusculaire induit par le rapacuronium, le rocuronium ou le cisatracurium à un ratio de 0,9 d'un TDQ, mesuré au niveau des AL, a été plus rapide avec l'administration d'édrophonium, comparée à la récupération spontanée.

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THE pharmacodynamics of neuromuscular block vary with the neuromuscular unit being evaluated. In general, however, the more centrally located muscles, such as those of the face and respiration, are relatively resistant to the effects of neuromuscular blocking agents.¹ With doses of nondepolarizing neuromuscular blocking agents that cause 100% neuromuscular block at the adductor pollicis (AP), the larynx does not necessarily develop that depth of block,² neither does the diaphragm.^{1,3,4} The more centrally located muscles also have a faster onset of and recovery from neuromuscular blockade than those that are located more peripherally.¹

Pharmacologic antagonism of neuromuscular block at the AP following the administration of any nondepolarizing relaxant at multiple varying depths of block, has been well characterized. The ease of antagonism appears to be, at least in part, dependent on the pharmacokinetics and pharmacodynamics of the neuromuscular blocking agents, with intermediate-acting agents being more readily antagonized than long-acting agents.⁵ Similarly, the depth of neuromuscular block at the time of administration of the anticholinesterase impacts on the time required for recovery of neuromuscular function in that more time is required for recovery from deeper levels of neuromuscular block than from less profound depths of block.^{6,7}

Typically, at the conclusion of an anesthetic, recovery of neuromuscular function is monitored at the AP. Recommendations for recovery of neuromuscular function have been based on recovery to a train-of-four (TOF) ratios of 0.7 to 0.9 at the AP.^{8,9} The clinician, though, is largely concerned about the patient's ability to protect his airway and breathe adequately.¹⁰ The musculature of the airway behaves differently to neuromuscular blocking agents than does the AP. Numerous studies have looked at the pharmacodynamics of neuromuscular blockade in the larynx during spontaneous recovery of neuromuscular function following the administration of any of several different neuromuscular blocking agents.^{2,11} None has, however, examined pharmacologically antagonized recovery of neuromuscular function in this muscle group. This study was designed to determine the nature of complete recovery of muscle strength in the laryngeal adductors (LA) following rapacuronium-, mivacurium-, rocuronium- and cisatracurium-induced block during spontaneous and pharmacologically augmented recovery of neuromuscular function.

Methods

After approval of the protocol by the Committee on Human Rights in Research at Weill Medical College of Cornell University, 104 male patients consented to

participate in this open-label study. Patients were ASA physical status I or II, 18–59 yr of age and scheduled to undergo minimally invasive elective urologic surgical procedures. Upon enrolling to participate in the study, patients were assigned based on computer generated numbers to one of eight study groups: rapacuronium 1.5 mg·kg⁻¹ and spontaneous recovery, rapacuronium 1.5 mg·kg⁻¹ and edrophonium, mivacurium 0.25 mg·kg⁻¹ and spontaneous recovery, mivacurium 0.25 mg·kg⁻¹ and edrophonium, rocuronium 0.9 mg·kg⁻¹ and spontaneous recovery, rocuronium 0.9 mg·kg⁻¹ and edrophonium, cisatracurium 0.15 mg·kg⁻¹ and spontaneous recovery or cisatracurium 0.15 mg·kg⁻¹ and edrophonium.

On arrival at the operating room, monitors as appropriate for routine anesthetic care (electrocardiogram, non-invasive blood pressure and pulse oximetry) were applied. Anesthesia was induced with midazolam (0.01–0.05 mg·kg⁻¹), fentanyl (2–8 µg·kg⁻¹) and propofol (2–2.5 mg·kg⁻¹) while patients received 100% oxygen through an anesthesia facemask. After loss of consciousness, the patient's trachea was intubated without a relaxant. General anesthesia was maintained with nitrous oxide (70%) in oxygen, a propofol infusion (100–200 µg·kg⁻¹·min⁻¹), and supplemental fentanyl and midazolam as clinically indicated. Ventilation was adjusted to maintain end-tidal carbon dioxide between 32 and 35 mmHg. Esophageal temperature was maintained above 35.5°C with a Bair Hugger (Augustine Medical, Eden Prairie, MN, USA) and warmed *iv* fluids.

The response of the LA to stimulation was determined with a variation of the technique described by Donati, Plaud and Meistelman.¹² The endotracheal tube was positioned with the cuff between the vocal cords. The cuff of the endotracheal tube was inflated with air to a baseline pressure of 10–12 mmHg. The pressure in the cuff of the endotracheal tube was measured with a saline-filled transducer (Hewlett Packard Transpac, Chicago, IL, USA) attached to the pilot balloon of the endotracheal tube with a stopcock. After zeroing the transducer, the pressure in the cuff of the endotracheal tube was monitored continuously on the operating room monitor and recorded on a chart recorder. As the baseline pressure in the cuff (the pressure measured between successive TOF stimuli) increased, small amounts of the gas mixture (air and nitrous oxide) were removed via the stopcock over the course of the study to maintain the baseline pressure. The recurrent laryngeal nerves were stimulated with TOF stimuli (2 Hz for 2 sec every 10 sec; Grass S88, Quincy MA, USA). Stimulating electrodes were placed bilaterally just superior and lateral to the thyroid carti-

lage. Response of the LA (bilateral adduction of the vocal cords) was measured as pressure changes in the inflated cuff of the endotracheal tube. This method of monitoring clearly indicated pressure changes in response to stimulation. It also indicated pressure changes due to variations in intrathoracic pressure. Ventilator settings were adjusted to minimize changes in peak inspiratory pressure while maintaining adequate ventilation. Patients in whom recorded changes in the pressure of the cuff were not interpretable, either due to interference of ventilation or movement of the endotracheal tube while adjusting the volume of gas in the cuff, were not included in the data analysis.

After stimulating the recurrent laryngeal nerves for at least three minutes, the assigned neuromuscular blocking agent was administered as a rapid *iv* bolus. With beginning recovery of neuromuscular function, the stimulus was changed to TOF every 20 sec. Once the first twitch (T1) in the TOF had recovered to 10% of control, patients randomized to the anticholinesterase-facilitated recovery group received edrophonium ($0.5 \text{ mg}\cdot\text{kg}^{-1}$) and atropine ($0.01 \text{ mg}\cdot\text{kg}^{-1}$).

The times to T1 recovery of 10%, 25%, 75% or 95% and TOF ratios of 40%, 70% and 90% were determined. Upon complete recovery of neuromuscular function at the LA, the cuff of the endotracheal tube was deflated and advanced such that it was distal to the vocal cords and the study was terminated. Anesthesia was continued as was necessary for the surgery and the anesthetic administered at that point was determined by the patient's anesthesiologist.

Statistical analysis was performed using StatView software for Windows (SAS Institute, Cary, NC, USA). Differences in recovery between spontaneous and edrophonium-facilitated groups were compared using the Student *t* test. Analysis of variance was used for multiple comparisons among the different relaxants. A *P* value of < 0.05 was considered statistically significant. If a significant *P* value was obtained in multiple comparisons, further group comparisons were made using Fisher PLSD post hoc test.

Results

There were no significant differences with regard to average age, weight and height of patients in any of the groups (Table I). Average depth of maximal block was similar in all patient groups (Table II).

The time from administration of relaxant to 10% recovery of T1 at the LA did not differ between the spontaneous and the edrophonium-facilitated recovery groups. In the rapacuronium, rocuronium and cisatracurium groups the times required for recovery of T1 at the LA to 95% of control (Figure 1) and TOF

TABLE I Comparative patients' demographic data between the spontaneous recovery group (SP) and the edrophonium-facilitated group (ED)

	<i>n</i>	<i>Age (y)</i>	<i>Weight (kg)</i>	<i>Height (cm)</i>
<i>Rapacuronium</i>				
SP	12	35.3 (6.1)	82.8 (14.0)	181.8 (11.9)
ED	13	36.3 (5.9)	80.0 (8.7)	179.5 (7.5)
<i>Mivacurium</i>				
SP	11	35.9 (7.3)	84.9 (11.4)	181.0 (10.2)
ED	10	34.3 (6.3)	80.9 (9.1)	186.9 (13.2)
<i>Rocuronium</i>				
SP	10	35.2 (7.5)	78.8 (8.2)	180.2 (11.3)
ED	10	36.8 (7.5)	82.1 (9.1)	182.6 (8.8)
<i>Cisatracurium</i>				
SP	10	34.9 (6.3)	82.1 (10.0)	179.5 (8.5)
ED	8	35.0 (6.3)	83.8 (13.9)	180.1 (6.8)

Data are presented as mean (SD). No significant difference between the spontaneous recovery group (SP) and the edrophonium-facilitated group (ED) in any category.

TABLE II Onset profiles following administration of neuromuscular blocking agent at the laryngeal adductors

	<i>n</i>	<i>Maximal block (%)</i>	<i>Onset (min)</i>
<i>Rapacuronium</i>			
SP	12	100.0 (0.0)	1.0 (0.2)
ED	13	99.3 (2.3)	1.0 (0.3)
<i>Mivacurium</i>			
SP	11	100.0 (0.0)	1.5 (0.3)
ED	10	100.0 (0.0)	1.6 (0.5)
<i>Rocuronium</i>			
SP	10	99.2 (2.2)	1.3 (0.8)
ED	10	100.0 (0.0)	1.1 (0.3)
<i>Cisatracurium</i>			
SP	10	100.0 (0.0)	1.7 (0.4)
ED	8	100.0 (0.0)	1.8 (0.5)

Data are presented as mean (SD). No significant difference between the spontaneous recovery group (SP) and the edrophonium-facilitated group (ED) in any category.

ratio to 0.7 or 0.9 (Figure 2) for edrophonium-facilitated recovery were significantly shorter than those for spontaneous recovery of neuromuscular function. As is also shown in Figures 1 and 2, recovery in the mivacurium group was not significantly shortened by the administration of edrophonium. Administration of edrophonium at 10% recovery of T1 shortened the time from T1 = 10% to recovery of a TOF ratio of 0.7 or 0.9 by 6.6 min (41%), and 7.0 min (27%), respectively, for rapacuronium, 13.3 min (48%) and 19.7 min (44%) for rocuronium, and 12.4 min (53%) and 10.9 min (31%) for cisatracurium.

FIGURE 1 Spontaneous and facilitated T1 recovery at the laryngeal adductors in patients receiving 1.5 mg·kg⁻¹ rapacurium (A), 0.25 mg·kg⁻¹ mivacurium (B), 0.9 mg·kg⁻¹ rocuronium (C) and 0.15 mg·kg⁻¹ cisatracurium (D). Data are presented as mean SD. • = spontaneous recovery; ° = edrophonium-facilitated recovery. **P* < 0.05 when compared to the spontaneous recovery group.

Table III shows the recovery intervals for rapacurium, rocuronium and cisatracurium-induced block. The early phase of recovery (as defined by recovery of T1 from 10–25% and from 25–75%) occurred more quickly in the edrophonium-facilitated recovery groups than the spontaneous recovery groups. No significant shortening of the later phases of recovery (as defined by T1 75–95% or TOF ratio 0.4–0.9) was observed.

Discussion

Pharmacologically augmented recovery of neuromuscular function in the LA remains unclear. Edrophonium, administered at T1 recovery of 10%, shortened recovery of neuromuscular function at the LA in patients receiving rapacurium, rocuronium or cisatracurium. The degree of shortening of recovery to a TOF ratio of 0.7 ranged from 41 to 53% and to a TOF ratio of 0.9 from 27 to 44% when compared to spontaneous recovery. Antagonism of mivacurium-induced block did not result in significant shortening of recovery of neuromuscular function.

Edrophonium did not appear to accelerate recovery from neuromuscular block throughout the process of recovery of neuromuscular function. Once T1 height

FIGURE 2 Spontaneous and facilitated recovery of the TOF ratios at the laryngeal adductors in patients receiving 1.5 mg·kg⁻¹ rapacurium (A), 0.25 mg·kg⁻¹ mivacurium (B), 0.9 mg·kg⁻¹ rocuronium (C) and 0.15 mg·kg⁻¹ cisatracurium (D). Data are presented as mean SD.

• = spontaneous recovery; ° = edrophonium-facilitated recovery. **P* < 0.05 when compared to the spontaneous recovery group.

reached approximately 75% of control, recovery of neuromuscular function plateaued and the rate of recovery became similar in the facilitated recovery and spontaneous recovery groups. The degree of influence of edrophonium on recovery may be more dependent on its peak effect, which occurs within one to three minutes^{13,14} after administration, than its duration of action (66 min)¹³ or *t*_{1/2}_R (110 min).¹⁴ It may be, additionally, restricted by a ceiling effect for antagonism.^{15,16} As has been described at the AP, facilitated early recovery at the LA may be due to competitive inhibition of neuromuscular blockade at the neuromuscular junction because of increased acetylcholine concentrations. More complete recovery may depend on elimination of the relaxant from the plasma.

Antagonism of profound mivacurium-induced block did not shorten recovery time in our study. In other studies,^{17–20} 0.1–1.0 mg·kg⁻¹ edrophonium, administered after recovery at the AP to 10% of baseline or less, shortened recovery to a TOF ratio ≥ 0.7 by approximately four to eight minutes. However, even this degree of shortening of recovery is not observed when antagonism is attempted at nearly complete block (1% of control).¹⁷ The efficacy of

TABLE III Recovery intervals from the time of 10% recovery at the laryngeal adductors

	<i>n</i>	<i>T1</i> 10–25%	<i>T1</i> 25–75%	<i>T1</i> 75–95%	<i>TOF</i> ratio 0.4–0.7	<i>TOF</i> ratio 0.7–0.9
<i>Rapacuronium</i>						
SP	12	2.3 (1.1)	8.9 (2.8)	8.4 (3.7)	8.5 (2.8)	12.5 (4.5)
ED	13	1.0 (0.9) *	6.7 (4.4)	6.3 (3.1)	7.9 (3.3)	10.0 (6.9)
<i>Mivacurium</i>						
SP	11	2.4 (1.0)	6.6 (2.0)	5.0 (2.0)	5.8 (3.3)	7.7 (4.0)
ED	10	1.1 (1.2)	7.0 (5.5)	5.3 (5.2)	4.4 (4.8)	8.2 (4.9)
<i>Rocuronium</i>						
SP	10	5.0 (2.4)	17.7 (7.3)	14.7 (8.6)	14.8 (7.2)	17.2 (8.3)
ED	10	6.1 (9.7)	7.3 (6.7) *	9.8 (5.4)	8.9 (7.5)	15.6 (10.2)
<i>Cisatracurium</i>						
SP	10	4.2 (1.3)	13.8 (4.9)	13.3 (13.8)	13.3 (4.5)	11.0 (4.5)
ED	8	1.2 (0.3) *	4.7 (4.2) *	4.8 (3.0)	6.6 (4.5)	11.2 (10.1)

Data are presented as mean (SD). *T1* = first twitch; *TOF* = train-of-four; SP = spontaneous recovery group; ED = edrophonium-facilitated group. **P* < 0.05 when compared to the SP.

edrophonium antagonism of mivacurium-induced block is less than that of vecuronium or d-tubocurarine and even doses larger than those used clinically may not antagonize the block completely.²¹ Edrophonium has been reported to transiently increase plasma concentrations of the two potent stereoisomers (trans-trans and cis-trans isomers) of mivacurium.²¹ Altered kinetics may result in a limited ability of edrophonium to effectively antagonize profound mivacurium-induced block.²¹ Edrophonium-induced desensitization of acetylcholine receptors²² appears not to be a factor as other neuromuscular blockers in our study could be antagonized.

We used a dose of 0.5 mg·kg⁻¹ edrophonium to antagonize profound residual neuromuscular block. Although this dose is sufficient to antagonize lesser degrees of block (i.e., *T1* > 25% at the AP),^{5,7,23,24} it has been reported that at least 1.0 to 1.5 mg·kg⁻¹ is needed for rapid restoration from vecuronium- or pancuronium-induced block when *T1* < 10% of control.⁵ The degree of spontaneous recovery prior to antagonism seems to be particularly important when edrophonium, rather than neostigmine, is used.^{5,23,25} Therefore, the dose used in this study may have been too low to evaluate the actual efficacy of early antagonism with this agent. A greater degree of antagonism may have been observed had the anticholinesterase been administered following a greater degree of spontaneous recovery or had a larger dose been administered. The dose chosen, however, appears to have been large enough to augment recovery and to identify relative differences in recovery with the relaxants studied. A bigger dose of anticholinesterase may have had no impact on recovery as even larger doses of edrophonium or neostigmine have been shown to have the same effect on recovery regardless of time of administration.^{26–28}

Whether or not what was observed in this study is applicable to other centrally located neuromuscular units remains to be determined. Certainly the pharmacodynamics of onset of and recovery from nondepolarizing neuromuscular blockade are different in the muscles of respiration when compared to the AP.^{1–4} These differences are likely due to the greater blood flow of these more centrally located muscles.²⁹ Whether or not differences in the pharmacodynamics of neuromuscular blocking agents exist between the different muscles of respiration has not been studied.

While pharmacologic antagonism of neuromuscular block was observed in the LA, it is not possible to conclude that it would have also been observed at the AP. While antagonism of rapacuronium-induced block is possible two to five minutes after administration of the relaxant,^{30,31} antagonism of profound levels of block induced with other neuromuscular blocking agents is not possible. In this study, though, rapacuronium did not stand out as being different from either cisatracurium or rocuronium in terms of ease of antagonism of block at the LA. The criteria for prompt antagonism of neuromuscular block at the AP may be not applicable at the LA. Acetylcholinesterase content and activity in the fast contracting muscles (LA) is greater than in the slow contracting muscles (AP).^{32,33} Therefore, responsiveness to anticholinesterases may differ between the LA and the AP.

It is important that recovery of strength in the musculature of the airway be achieved prior to extubation of a patient's trachea as *TOF* ratios of 60 to 80% at the AP have been associated with a decreased hypoxic drive to breathe and an increased incidence of aspiration.^{34–36} Further investigations specifically comparing recovery in the LA to that in the AP may be warranted.

In conclusion, rapacuronium-, rocuronium- or cisatracurium-induced neuromuscular block at the LA was effectively antagonized by edrophonium, 0.5 mg·kg⁻¹. As has been described following antagonism of profound neuromuscular block at the AP, a more rapid rate of recovery at the LA was observed only in the early phase of antagonism. If timing of administration of an anticholinesterase is chosen based on the response of the AP to neuromuscular stimulation, the clinician can be confident that antagonism of block at the LA will also occur.

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