Dose-response relationships for edrophonium and neostigmine antagonism of atracurium and cisatracurium- induced neuromuscular block

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Purpose: To study the dose-response relationships for neostigmine and edrophonium during antagonism of neuromuscular block induced by atracurium and cisatracurium.

Methods: One hundred and twenty eight, ASA group 1 or 2 adults were given either 0.5 $mg \cdot kg^{-1}$ atracurium or 0.1 $mg \cdot kg^{-1}$ cisatracurium during fentanyl-thiopental-nitrous oxide-isoflurane anesthesia. The neuromuscular block was measured by an acceleration-responsive transducer. Responses were defined in terms of percent depression in the first twitch (T1) and train-of-four (TOF) response. When spontaneous recovery of first twitch height reached 10% of its initial control value, edrophonium (0.1, 0.2, 0.4, or 1 $mg \cdot kg^{-1}$) or neostigmine (0.005, 0.01, 0.02, or 0.05 $mg \cdot kg^{-1}$) was administered by random allocation. Neuromuscular function in another sixteen subjects was allowed to recover spontaneously.

Results: At five minutes, unlike edrophonium, neostigmine was equally effective against atracurium and cisatracurium with respect to T1 recovery. The neostigmine T1-ED_{50} was 10.3 ± 1.06 (SEM) $\mu g \cdot kg^{-1}$ after atracurium and 11.2 ± 1.06) $\mu g \cdot kg^{-1}$ after cisatracurium. The edrophonium ED_{50} was 157 ± 1.07 $\mu g \cdot kg^{-1}$ with atracurium and 47.4 ± 1.07 $\mu g \cdot kg^{-1}$ with cisatracurium, giving a neostigmine:edrophonium potency ratios of 15.2 ± 1.7 and 4.2 ± 0.41 ($P < 0.001$) for atracurium and cisatracurium, respectively. At 10 min neostigmine was 13 ± 1.4 times as potent as edrophonium for achieving 50% TOF recovery after atracurium paralysis. After cisatracurium the potency ratio was 11.8 ± 1.3 (NS).

Conclusions: Although there were differences at five minutes, neostigmine:edrophonium potency ratios at 10 min, were similar in both relaxants studied.

Objectif : Étudier les relations doses-réponses de la néostigmine et de l'édrophonium pendant le renversement du bloc neuromusculaire induit par l'atracurium et le cisatracurium.

Méthode : Cent vingt-huit adultes, d'état physique ASA I ou II, ont reçu, soit 0,5 $mg \cdot kg^{-1}$ d'atracurium, soit 0,1 $mg \cdot kg^{-1}$ de cisatracurium pendant l'anesthésie au fentanyl-thiopental-protoxyde d'azote-isoflurane. Le bloc neuromusculaire a été mesuré par un transducteur sensible à l'accélération. Les réponses ont été définies en termes de pourcentage de dépression lors de la réponse à la première stimulation (T_1) et au train-de-quatre (TDQ). Au moment où la récupération spontanée à la première stimulation a atteint 10 % de la valeur témoin initiale, de l'édrophonium (0,1; 0,2; 0,4 ou 1 $mg \cdot kg^{-1}$) ou de la néostigmine (0,005; 0,01; 0,02 ou 0,05 $mg \cdot kg^{-1}$) a été administrée selon une affectation aléatoire. Chez seize autres sujets, on a laissé la fonction neuromusculaire se rétablir spontanément.

Résultats : À cinq minutes, contrairement à l'édrophonium, la néostigmine a été également efficace contre l'atracurium et le cisatracurium quant à la récupération à T_1. La T_1-ED_{50} de la néostigmine était de 10,3 ± 1,06 (erreur type) $\mu g \cdot kg^{-1}$ après l'atracurium et de 11,2 ± 1,06 $\mu g \cdot kg^{-1}$ après le cisatracurium. La ED_{50} de l'édrophonium était de 157 ± 1,07 $\mu g \cdot kg^{-1}$ avec l'atracurium et de 47,4 ± 1,07 $\mu g \cdot kg^{-1}$ avec le cisatracurium, ce qui donnait des coefficients de puissance néostigmine:édrophonium de 15,2 ± 1,7 et de 4,2 ± 0,41 ($P < 0,001$) pour l'atracurium et le cisatracurium, respectivement. À 10 min, la néostigmine était 13 ± 1,4 fois aussi puissante que l'édrophonium pour atteindre 50 % de récupération du TDQ après la paralysie avec l'atracurium. Après l'utilisation de cisatracurium, le coefficient de puissance était de 11,8 ± 1,3 (NS).

Conclusion : Même s'ils étaient différents à cinq minutes, les coefficients de puissance néostigmine:édrophonium ont été similaires à 10 min avec les deux relaxants étudiés.

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CISATRACURIUM (1R-Cis, 1'R-Cis) is approximately four to five times more potent than atracurium (based on their respective ED_{95} values) and has a similar neuromuscular blocking profile to atracurium except for a slower onset.[1,2] Detailed studies of antagonism of cisatracurium are lacking.

The comparative dose-response relationships for edrophonium and neostigmine after atracurium and cisatracurium have not been studied. Therefore, this study was designed to establish dose-response relationships for edrophonium and neostigmine as antagonists of atracurium and cisatracurium block.

Patients and methods

After obtaining institutional approval and informed consent, we studied 144 ASA physical status I or II patients of both sexes, aged 18-52 (28.8 ± 8.3 [mean ± SD]) yr, weighed 41-100 (71.5 ± 12.8) kg and were 146-191 (169.6 ± 8.3) cm in height. All patients were undergoing elective procedures, had no neuromuscular, renal or hepatic disease, and were not taking any drug known to interfere with neuromuscular function. All patients received 2 mg lorazepam *po* 90 min preoperatively. An infusion of lactated Ringer's solution was given *iv* before induction of anesthesia. The ECG, pulse oximetry and arterial blood pressure were monitored and the peripheral temperature was maintained > 32.5°C and central temperature > 36°C. Anesthesia was induced with 2 $\mu g \cdot kg^{-1}$ fentanyl and 3-5 $mg \cdot kg^{-1}$ thiopental and was maintained with nitrous oxide 60% and isoflurane, 1.2% inspired, in oxygen. Concentrations of isoflurane, nitrous oxide, oxygen, and carbon dioxide were measured continuously by a multiple-gas analyzer (Capnomac, Datex Instrumentarium Corporation, Helsinki, Finland). Ventilation was adjusted to maintain normocapnia ($P_{ET}CO_2$ - 4.6-5.3 kPa).

The acceleration transducer, 5 × 10 mm in size and weighing 20 g, is a piezoelectric ceramic wafer with an electrode on each side (Biometer International, Odense, Denmark) that was fastened to the volar side of the interphalangeal joint of the thumb.[3,4] When the wafer experiences acceleration, a voltage difference develops between the two electrodes, and this voltage can be measured and recorded directly. The ulnar nerve was stimulated supramaximally at the wrist with square pulses of 0.2 msec duration, delivered in a train-of-four (TOF) sequence at 2 Hz every 15 sec. Free movement during evoked thumb adduction was allowed by fixation of the extended four ulnar fingers by an adhesive tape. On stimulating the ulnar nerve, the transducer was set in motion, and a voltage developed that was proportional to the acceleration. The resulting electrical signal was analyzed by the Accelograph (Biometer International). The TOF values were displayed and recorded. The first twitch (T1) of the TOF was considered the twitch height.

After establishment of a stable neuromuscular response, patients were randomly divided into two groups (n= 72 in each) to receive either 0.5 $mg \cdot kg^{-1}$ atracurium or 0.1 $mg \cdot kg^{-1}$ cisatracurium *iv* a free-flowing bolus dose. Tracheal intubation was performed when neuromuscular response was abolished. Additional increments of 0.1 $mg \cdot kg^{-1}$ atracurium or 0.02 $mg \cdot kg^{-1}$ cisatracurium *iv* were given to patients who required continued muscular relaxation, whenever the first twitch recovered to 10% of control value.

At the end of surgery, when first twitch height (T1; the first response in the TOF) had recovered to 10% of the control value, the patients received edrophonium, 0.1, 0.2, 0.4, or 1 $mg \cdot kg^{-1}$, neostigmine, 0.005, 0.01, 0.02, or 0.05 $mg \cdot kg^{-1}$, or no reversal drug (n = 8 in each subgroup) by random allocation. Atropine, 0.3-1.5 mg, was administered when appropriate. No other antagonist was given for at least 10 min and the inspired isoflurane concentration was not altered. The TOF ratio (the amplitude of the fourth evoked response as a fraction of the first evoked response: T4/T1) was recorded continuously over the subsequent 10 min, at which point the dose-response study was concluded. An additional dose of antagonist was given after 10 min if the train-of-four ratio was < 0.75 or if the patients had clinical signs of inadequate neuromuscular function.

The results were subjected to probit transformation using PCNONLIN version 4.1 (ClinTrials, Inc., Lexington, Kentucky).[5] Dose-response relationships were calculated by linear regression of the probit transformation of T1 and TOF ratio on the logarithm of the dose. From these, the doses of antagonist expected to produce 50% and 80% recovery (ED_{50} and ED_{80}) of T1 and TOF ratio were obtained at 5 and 10 min after the administration of the drug. Regression lines were compared using analysis of covariance. First, we tested the lines to determine if they deviated from parallelism, if they did not, an F test was applied to determine if the elevations were different. If so, a t test was applied to determine which line differed in elevation,[5] using BMDP statistical package (University of California Press, 1990). Comparisons were made between the potencies of the antagonist drugs.[6] Recovery times were compared using analysis of variance. Dunnett's test was used to compare the spontaneous recovery group with each of the other groups. When a specific recovery was not reached in the control group, the Student-Newman-Keuls multiple

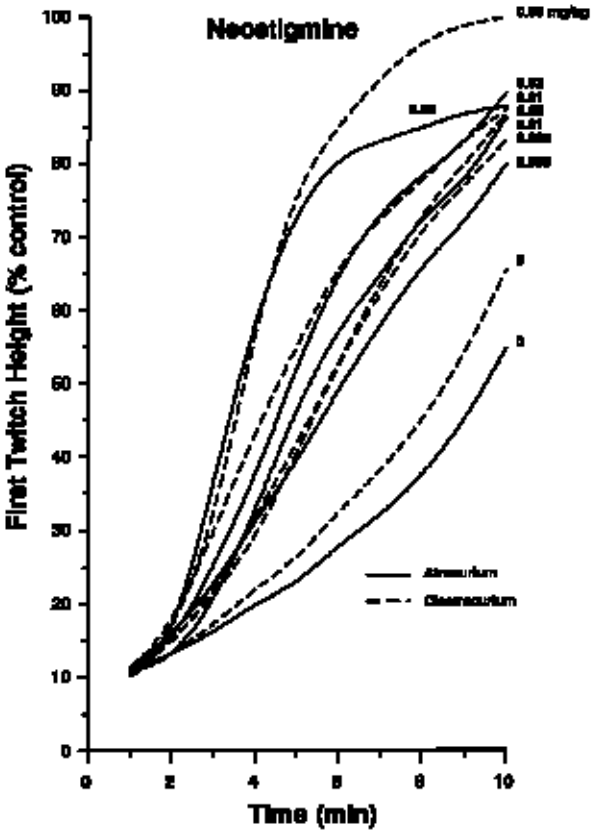

FIGURE 1 Mean first twitch height *vs* time after administration of various doses of neostigmine. Antagonism of neuromuscular blockade was attempted when first twitch height reached 10% of its control value. The neuromuscular blockers used were either atracurium or cisatracurium. Confidence intervals were omitted for the sake of clarity.

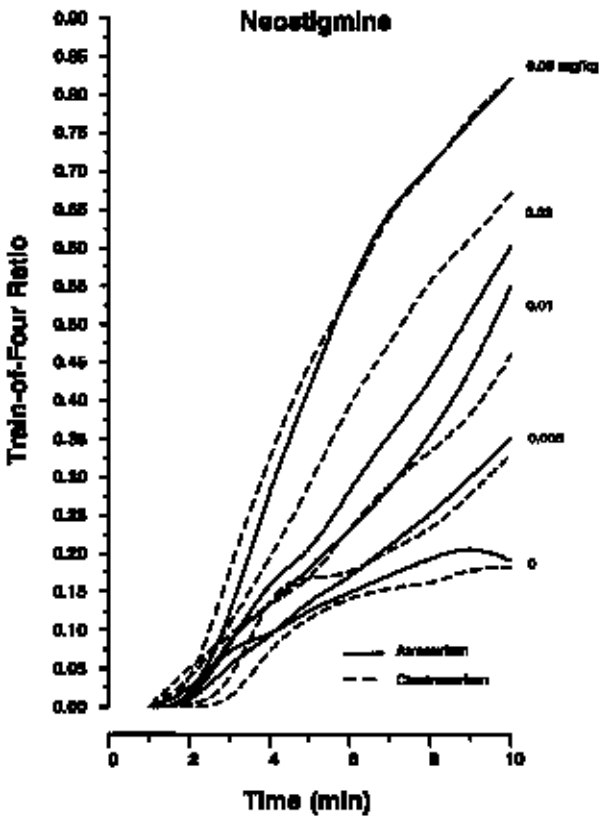

FIGURE 2 Mean train-of-four ratio *vs* time after administration of various doses of neostigmine. Antagonism of neuromuscular blockade was attempted when first twitch height reached 10% of its control value. The neuromuscular blockers used were either atracurium or cisatracurium. Confidence intervals were omitted for the sake of clarity.

range test was used for comparisons. Unless otherwise specified, results were expressed as means and 95% confidence intervals, and were considered statistically significant when the *P* value was 0.05 or less.

Results

The final responses of T1 were within 15% of the initial control values. The TOF final responses never exceeded unity. Figures 1-4 show first twitch height and train-of-four ratio as a function of time after administration of the antagonist. At all doses, the effect of edrophonium was rapid and sustained, neostigmine had a slower onset. The degree of recovery increased with time after administration of the reversal drug and with dose given.

In the absence of antagonist, the spontaneous recovery for the first 10 min following return to 10% first twitch height, T1 and TOF proceeded at similar rates with both relaxants (Figures 1-4, Table I). Mean first twitch height reached 50 (CI 40-70) and 66 (60-72) for atracurium and cisatracurium, respectively. Corresponding TOF ratios were 0.19 (0.1-0.3) and 0.18 (0.09-0.26), respectively (NS).

Train-of-four recovery 10 min after reversal was greater ($P < 0.01$) in those patients who received either edrophonium, or neostigmine than those who were allowed to recover spontaneously (Table I). Similar observations were noted for the first twitch recovery with atracurium (Table I). Likewise, times taken for the twitch height to recover from 10-25% and 25-75% of the control value were longer in the spontaneous recovery group than in the other groups (Table I). Patients who received either 0.05 $mg \cdot kg^{-1}$ neostigmine or 1.0 $mg \cdot kg^{-1}$ edrophonium recovered to a TOF ratio of 0.75 within 10 min.

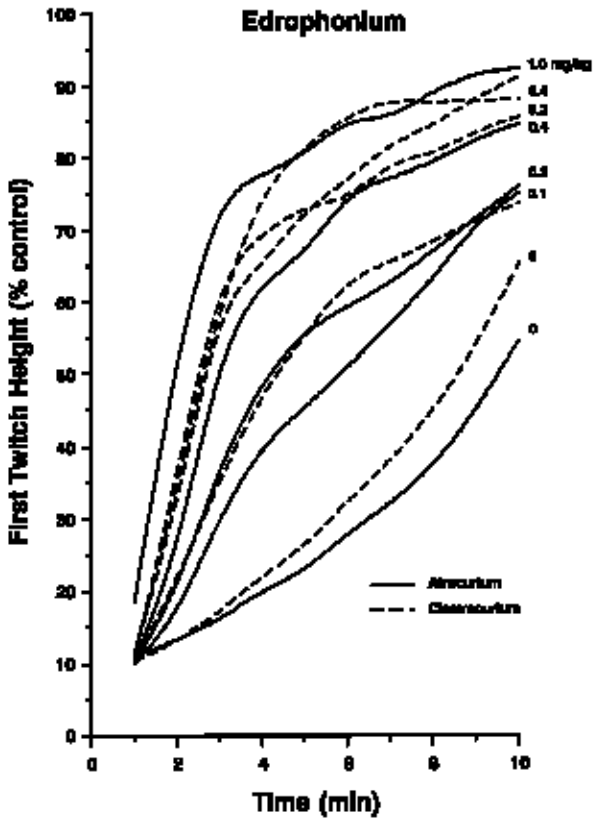

FIGURE 3 Mean first twitch height *vs* time after administration of various doses of edrophonium. Antagonism of neuromuscular blockade was attempted when first twitch height reached 10% of its control value. The neuromuscular blockers used were either atracurium or cisatracurium. Confidence intervals were omitted for the sake of clarity.

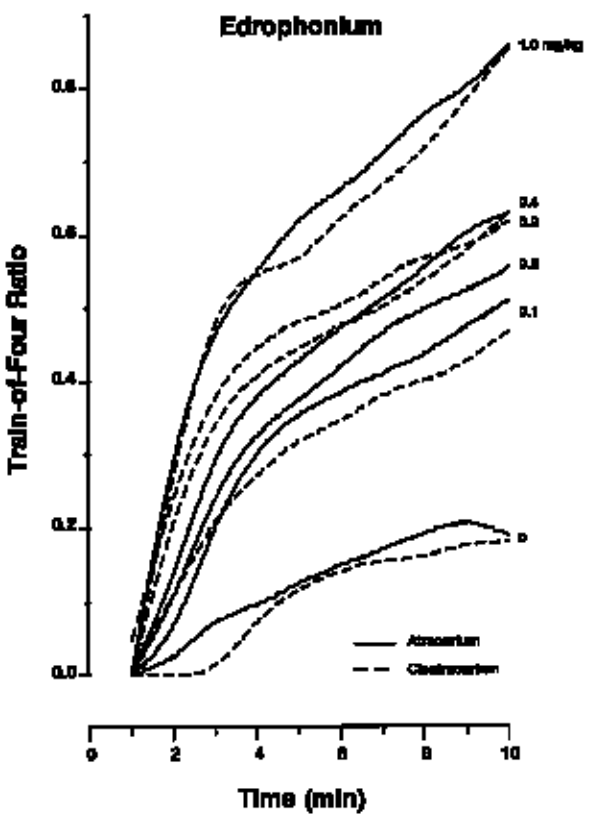

FIGURE 4 Mean train-of-four ratio *vs* time after administration of various doses of edrophonium. Antagonism of neuromuscular blockade was attempted when first twitch height reached 10% of its control value. The neuromuscular blockers used were either atracurium or cisatracurium. Confidence intervals were omitted for the sake of clarity.

The dose-response relationships for the T1 and TOF responses at 5 and 10 min are shown in Figures 5 and 6, respectively. For each relaxant-antagonist pair, the lines constructed at 10 min were shifted to the left from those constructed at five minutes ($P < 0.001$), indicating a more complete antagonism with time. Except for lines describing TOF curves with edrophonium-cisatracurium pair at five minutes, the slopes of the lines describing first twitch and train-of-four recovery after edrophonium were not different from the corresponding lines after neostigmine.

The ED_{50} and ED_{80} values for neostigmine and edrophonium were derived from the dose-response curves (Tables II, III). The potency ratios, or the potency of neostigmine expressed as a multiple of that of edrophonium are presented in Tables II and III. For the train-of-four ED_{50} values, the potency ratio increased with time (Table III). At 10 min neostigmine was 13 (1.4) times as potent as edrophonium for achieving 50% TOF recovery after atracurium paralysis. After cisatracurium the potency ratio was 11.8 ± 1.3 (NS).

The dose-response curves were used to estimate the effects of 0.02 and 0.04 $mg \cdot kg^{-1}$ neostigmine and 0.5 and 1.0 $mg \cdot kg^{-1}$ edrophonium (Table IV). Edrophonium was more effective with cisatracurium first twitch recovery at five minutes only. Train-of-four recovery was similar in both neuromuscular blockers after edrophonium or neostigmine.

Discussion

This study demonstrated that 0.1-1.0 $mg \cdot kg^{-1}$ edrophonium and 0.005-0.05 $mg \cdot kg^{-1}$ neostigmine produced dose-dependent reversal of atracurium or cisatracurium-induced neuromuscular block. Ten

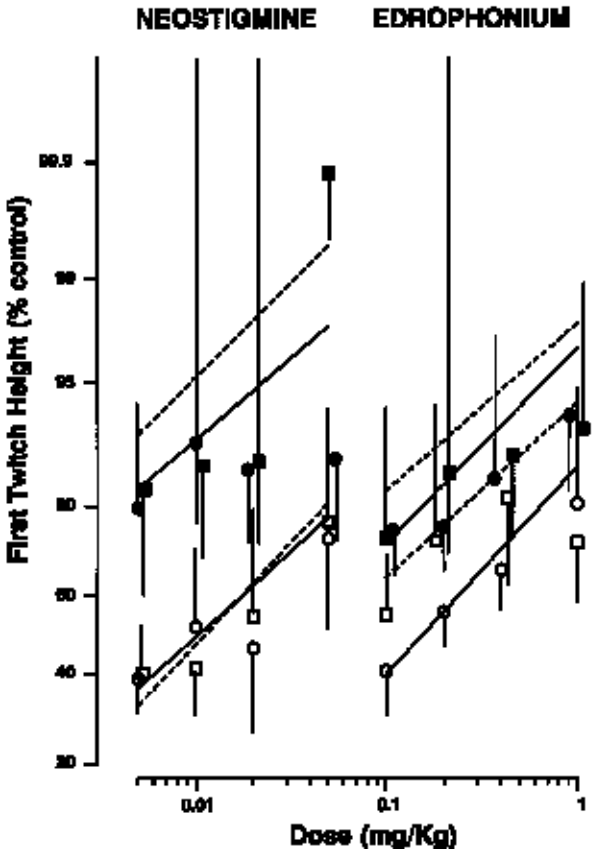

FIGURE 5 Dose-response relationships of first twitch recovery (% control) obtained at five minutes and 10 min after administration of neostigmine or edrophonium. Individual points represent mean T1 attained with each dose and the bars represent 95% confidence intervals.
○———○ = Atracurium at five minutes.
●———● = Atracurium at 10 min.
•·····• = Cisatracurium at five minutes.
■·····■n = Cisatracurium at 10 min.

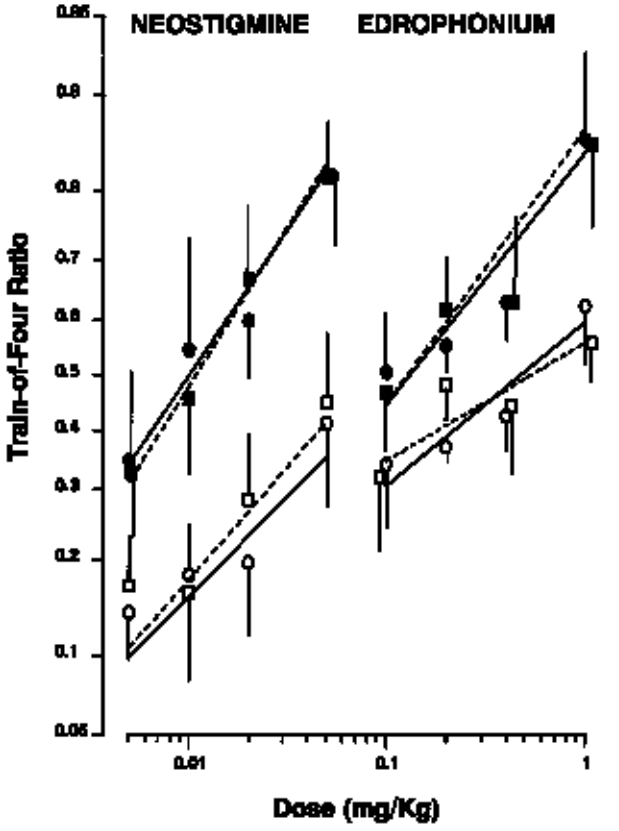

FIGURE 6 Dose-response relationships of train-of-four recovery obtained at five minutes and 10 min after administration of neostigmine edrophonium. Individual points represent mean TOF ratio attained with each dose and the bars represent 95% confidence intervals.
○———○ = Atracurium at five minutes.
●———● = Atracurium at 10 min.
•·····• = Cisatracurium at five minutes.
■·····■n = Cisatracurium at 10 min.

minutes after reversal, TOF ED_{50} of neostigmine or edrophonium antagonism of atracurium was similar to that of cisatracurium. When the effect of the first twitch was examined, edrophonium appeared relatively more potent after cisatracurium than after atracurium only at five minutes. Our data also indicated that potency ratios were not the same for single twitch and train-of-four responses.

Atracurium, a benzylisoquinolinium diester, is comprised of a mixture of 10 geometric isomers with different clearance rates and terminal half-lives.[7,8] Cisatracurium, one of the 10 stereoisomers of atracurium, has the 1R-Cis, 1'R-Cis configuration. This isomer comprises approximately 15% of the atracurium mixture.[9] Cisatracurium is approximately four to five times more potent than atracurium (based on their respective ED_{95} values), has a similar neuromuscular blocking profile to atracurium except for a slower onset.[1,2] The pharmacokinetics of cisatracurium are similar to those of atracurium.[11,12] Its clearance is 5 $ml \cdot kg^{-1} \cdot min^{-1}$, its elimination half-life is 23 min and its volume of distribution at steady state is approximately 150 $ml \cdot kg^{-1}$.[12] Although atracurium undergoes ester hydrolysis as well as Hofmann elimination and end-organ dependent elimination,[13–15] cisatracurium undergoes only Hofmann elimination to form laudanosine and monoquaternary acrylate.[12,16]

TABLE I First twitch (T1) and train-of four (TOF) recovery from 10% block (mean (95% CI or range*)).

Group	n	T1 at 10 min (% control)	TOF ratio At 10 min	Times to T1 recovery (min) n	10-25%	n	25-75%	Time to TOF recovery (min) n	0.25-0.75
Atracurium									
Spontaneous recovery	8	55 (40-70)	0.19 (0.1-0.3)	8	4.4 (2.8-5.9)	3	5.8 (4.8-6.8)	0	—
Neostigmine (mg·kg^{-1})									
0.005	8	80 (67-93) †	0.35 (0.18-0.52)	8	2.6 (2.3-2.9)†	8	5.7 (4.6-6.8)	5	5.5 (2.6-8.4)
0.01	8	90 (77-103)†	0.55 (0.38-0.71)†	8	2.1 (1.6-2.6)†	8	4.5 (2.7-6.3)‡	6	5.6 (4.1-6.9)
0.02	8	86 (72-100)†	0.60 (0.52-0.68)†	8	2.2 (1.8-2.6)†	8	4.1 (2.9-5.3)‡	8	5.7 (4.6-6.8)
0.05	8	88 (73-103)†	0.82 (0.74-0.90)†	6	1.4 (0.9-1.9)†	6	1.9 (0.5-3.3)‡	8	3.2 (2.4-4.0)‡
Edrophonium (mg·kg^{-1})									
0.1	8	75 (65-85)	0.51 (0.43-0.59)†	8	1.5 (1.3-1.7)†	7	6.8 (3.2-10.4)	6	9.0 (7.1-10.9)‡
0.2	8	76 (66-86)†	0.56 (0.48-0.64)†	8	1.1 (0.8-1.4)†	7	7.7 (5.8-9.6)	6	9.2 (8.4-10.0)‡
0.4	8	85 (72-98)†	0.63 (0.55-0.71)†	8	0.9 (0.7-1.1)†	8	4.4 (2.6-6.2)	5	7.1 (5.2-8.9)
1.0	8	93 (85-101)†	0.86 (0.78-0.94)†	8	1.0 (0.7-1.3)†	8	2.5 (0.9-4.1)‡	8	5.0 (3.4-6.6)
Cisatracurium									
Spontaneous recovery	8	66 (60-72)	0.18 (0.09-0.26)	8	3.6 (2.9-4.3)	2	7.1 (6.0-8.2)*	0	—
Neostigmine (mg·kg^{-1})									
0.005	8	83 (60-106)	0.33 (0.25-0.41)†	8	2.6 (1.7-3.5)†	8	5.2 (4.0-6.4)	5	5.9 (2.8-9.0)
0.01	8	87 (70-104)	0.46 (0.29-0.63)†	8	2.3 (1.6-2.9)†	8	5.4 (4.3-6.5)	8	6.3 (4.9-7.7)
0.02	8	87 (72-102)	0.67 (0.59-0.75)†	8	1.6 (1.2-2.0)†	8	3.4 (2.6-4.2)‡	8	6.2 (5.1-7.3)
0.05	8	99.8 (99.5-100)†	0.82 (0.74-0.90)†	8	1.7 (1.3-2.1)†	8	2.4 (1.7-3.2)‡	8	4.6 (3.2-6.0)
Edrophonium (mg·kg^{-1})									
0.1	8	74 (55-93)	0.47 (0.39-0.55)†	8	1.2 (0.9-1.5)†	8	6.5 (3.5-9.5)	6	8.1 (4.9-11.2)
0.2	8	86 (70-102)	0.62 (0.54-0.70)†	6	0.9 (0.6-1.2)†	6	1.3 (0.7-1.9)‡	7	6.9 (3.0-10.8)
0.4	8	88 (72-104)	0.63 (0.46-0.79)†	7	1.0 (0.6-1.4)†	7	1.4 (0.7-2.1)‡	8	7.0 (5.8-8.3)
1.0	8	91 (84-99)†	0.86 (0.78-0.94)†	8	0.8 (0.6-0.9)†	8	2.6 (1.5-3.7)	8	5.3 (4.1-6.5)

†P <0.05 compared with the spontaneous recovery group (Dunnett's test).

‡P <0.05 within group comparisons (Student-Newman-Keuls multiple range test).

TABLE II Doses of edrophonium or neostigmine (μg·kg^{-1}) required for 50% (ED_{50}) and 80% (ED_{80}) recovery of first twitch height 5 min after injection of the antagonists

	Atracurium	*Cisatracurium*	*P*
ED_{50}			
Edrophonium	157 (1.07)	47.4 (1.07)	<0.0001
Neostigmine	10.3 (1.06)	11.2 (1.06)	0.5
Potency ratio	15.2 (1.7)	4.2 (0.4)	<0.0001
ED_{80}			
Edrophonium	657 (1.07)	259 (1.07)	<0.0001
Neostigmine	58.5 (1.06)	49 (1.06)	<0.0001
Potency ratio	11.2 (0.2)	5.3 (0.1)	<0.0001

Values are mean (SEM) of estimate for the mean.

TABLE III Doses of edrophonium or neostigmine (μg·kg^{-1}) required for 50% (ED_{50}) train-of-four recovery 5 and 10 min after injection of the antagonists

	Atracurium	*Cisatracurium*	*P*
5 min			
ED_{50}			
Edrophonium	472 (1.05)	526 (1.06)	<0.0001
Neostigmine	126 (1.06)	80 (1.2)	<0.0001
Potency ratio	3.7 (0.03)	6.6 (0.1)	<0.0001
10 min			
ED_{50}			
Edrophonium	130 (1.07)	127 (1.07)	0.052
Neostigmine	10 (1.06)	10.7 (1.2)	0.6
Potency ratio	13 (1.4)	11.8 (1.3)	0.5

Values are mean (SEM) of estimate for the mean.

In this study, spontaneous recovery for the first 10 min following return to 10% first twitch height, T1 and TOF proceeded at similar rates with atracurium and cisatracurium (Figures 1-4 and Table I). Similarly, Smith and colleagues[17] reported that recovery times after a bolus dose of atracurium 0.5 mg·kg^{-1} or cisatracurium 0.1 mg·kg^{-1} were similar. We also noted that at five minutes edrophonium was more effective in reversing twitch depression induced by cisatracurium than atracurium (Table II). In contrast, neostigmine was more effective in reversing a TOF response previously depressed by cisatracurium than atracuri-

TABLE IV Effect on T1 and T4/T1 of two doses of edrophonium and neostigmine 5 and 10 min after injection

	Edrophonium (μg·kg⁻¹)		*Neostigmine (μg·kg⁻¹)*	
	0.5	*1.0*	*0.02*	*0.04*
Atracurium				
First twitch height (% of control)				
5 min	75 (73-77)	86 (84-88)	63 (61-64)	74 (72-77)
10 min	93 (92-94)	97 (96-98)	94 (93-95)	97 (96-98)
Train-of-four ratio (%)				
5 min	51 (49-53)	60 (57-63)	23 (21-25)	32 (29-35)
10 min	75 (73-77)	85 (82-87)	66 (64-67)	79 (77-81)
Cisatracurium				
First twitch height (% of control)				
5 min	88 (86-89)	93 (92-95)	63 (61-65)	77 (74-79)
10 min	95 (94-96)	98 (97-99)	98 (97-99)	99 (98.8-99.5)
Train-of-four ratio (%)				
5 min	50 (47-52)	56 (53-59)	27 (21-32)	38 (33-43)
10 min	77 (76-79)	87 (85-89)	65 (59-71)	80 (76-83)

Values are mean (95% CI).

um. In accordance with our results, Smith and colleagues[18] reported that neostigmine was more effective in reversing a TOF response previously depressed by vecuronium than atracurium. However, for TOF recovery at 10 min, the potency ratio of both antagonists was not different in both relaxants studied (Table III). Our data also indicate that the potency ratio was not the same for single twitch and TOF. For instance, when the reversal was attempted at 10% T1 recovery from cisatracurium block, 4.2 times as much edrophonium as neostigmine was required to achieve 50% T1, but 6.6 times as much is needed to reach a TOF ratio of 0.5 (Tables II, III). In this respect, our results are consistent with our previously published results and those of other investigators[17–23] who reported similar observations with other non-depolarizing neuromuscular blockers.

The reported neostigmine:edrophonium potency ratio for train-of-four, 10 min after injection of the antagonist (following return to 10% first twitch height) was 10.4 for mivacurium,[20] 13.5 for atracurium,[22] 26 for vecuronium,[18] 27.5 for rocuronium,[19] 24 for pancuronium and 29 for tubocurarine.[23] The corresponding potency ratios of atracurium and cisatracurium noted in this study were 13 and 11.8, respectively (Table III). Further, the potency ratio was relatively small shortly after reversal, but the discrepancy between the potencies of neostigmine and edrophonium increased with time. This could be explained by the fact that edrophonium has a more rapid onset of action than neostigmine. Evidence suggests that the direct influences of the acetylcholinesterase drugs on neuromuscular transmission involve at least three distinct, although possibly interacting mechanisms: (a) a weak agonist action, (b) the formation of desensitized receptor-complex intermediates, and (c) the alteration of the conductance properties of active channels.[24] Therefore, the pharmacological actions of neostigmine and edrophonium are not limited to enzyme inhibition.

Our data also confirm that the neostigmine:edrophonium potency ratio varies depending on the relaxant used. For example, 0.04 mg·kg^{-1} neostigmine is expected to produce a T1 of 97% and 99% after 10 min if given after atracurium and cisatracurium, respectively (Table IV). Corresponding values noted by others were 95%, 99%, 86%, 77%, and 76% after atracurium, vecuronium,[18] rocuronium,[19] pancuronium, and tubocurarine,[23] respectively. With 0.5 mg·kg^{-1} edrophonium the corresponding values would be 89%, 86%, 74%, 79%, and 68%, respectively. In this study, 0.5 mg·kg^{-1} edrophonium is expected to produce a T1 of 93% and 95% after 10 min if given after atracurium and cisatracurium, respectively (Table IV).

The effect of 0.04 mg·kg^{-1} neostigmine on TOF ratio is expected to be 0.79 and 0.80 after 10 min if given after atracurium and cisatracurium, respectively (Table IV). Corresponding values were 0.67, 0.67, 0.74, 0.60, and 0.49 after atracurium, vecuronium,[18] rocuronium,[19] pancuronium, and tubocurarine,[23] respectively. With 0.5 mg·kg^{-1} edrophonium the corresponding values would be 0.61, 0.53, 0.51, 0.30, and 0.32, respectively. In this study, 0.5 mg·kg^{-1} edrophonium is expected to produce a TOF ratio of 0.75 and 0.77 after 10 min if given after atracurium and cisatracurium, respectively (Table IV).

In conclusion, during thiopental-fentanyl-nitrous oxide-isoflurane anesthesia, when the reversal was attempted at 10% recovery of the first twitch height

from atracurium or cisatracurium-induced block, this study demonstrated that both neostigmine and edrophonium were able to produce dose dependent antagonism of both neuromuscular blockers. Except for lines describing TOF curves with edrophonium-cisatracurium pair at five minutes, the slopes of the lines describing first twitch and train-of-four recovery after edrophonium were not significantly different from the corresponding lines after neostigmine. The potency ratio was not the same for single twitch and train-of-four. However, for TOF recovery at 10 min, the potency ratio of both antagonists was similar in both atracurium and cisatracurium.

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