Accelerated reversal of atracurium blockade with divided doses of neostigmine

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The hypothesis that administration of neostigmine in divided doses might accelerate the antagonism of neuromuscular blockade was investigated. Neostigmine 0.05 mg·kg^{-1} was administered either in a single bolus dose (Group I, n = 16) or in an initial dose of 0.01 mg·kg^{-1} followed three minutes later by 0.04 mg·kg^{-1} (Group II, n = 16) for antagonism of atracurium-induced blockade. Reversal was attempted at 10 per cent spontaneous recovery of twitch height. The mean time (±SD) from the first injection of the drug until the train-of-four (TOF) ratio value had reached 0.75 was significantly shorter in Group II ($p < 0.05$) than in Group I (391.8 ± 83.3 and 468.6 ± 150.3 seconds respectively). The rate of TOF ratio recovery was 2.5 times faster after neostigmine administration in divided doses.

It is concluded that administration of neostigmine in divided doses, as described in this study, produced a significantly faster reversal of residual atracurium-induced neuromuscular blockade as compared to a single bolus administration.

Key words
NEUROMUSCULAR RELAXANTS: atracurium; ANTAGONISTS, NEUROMUSCULAR RELAXANTS: neostigmine; NEUROMUSCULAR TRANSMISSION: train-of-four.

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CAN ANAESTH SOC J 1986 / 33: 6 / pp 723–8

It has been demonstrated that the onset of the neuromuscular blockade can be accelerated significantly when the bolus dose of a non-depolarising muscle relaxant is preceded by a small "priming" dose of the same or a different non-depolarising agent.[1–6] Whether the administration of acetylcholinesterase inhibitors in a similar fashion will result in an accelerated recovery of neuromuscular function is not known.

Several investigators recommended titrating the dose of acetylcholinesterase inhibitors.[7] In one study, Miller *et al.*[8] administered neostigmine 0.25 mg every three minutes until recovery of the neuromuscular function was achieved. However, Payne *et al.*[9] reported that the administration of a second dose of 2.5 mg neostigmine caused reduction in the peak tetanic contraction and tetanic fade.

The present study was undertaken to investigate the reversal characteristics following administration of neostigmine in divided doses.

Methods

After institutional approval, 32 ASA physical status I or II patients undergoing minor elective procedures were studied. All patients were free from neuromuscular, renal or hepatic disease and were not taking any drugs known to interfere with neuromuscular function. Informed consent was obtained. All patients were premedicated with 0.15 mg·kg^{-1} diazepam orally 90 minutes preoperatively.

An intravenous infusion of lactated Ringer's solution in five per cent dextrose was established prior to induction. The ECG and nasopharyngeal temperature were monitored continuously by a Medishield M1 monitor. Blood pressure was mea-

sured every five minutes by an electronic oscillotonometer (Dinamap).

In all patients, anaesthesia was induced with fentanyl 2 $\mu g \cdot kg^{-1}$, thiopentone 5 $mg \cdot kg^{-1}$ and was maintained with 70 per cent nitrous oxide in oxygen and halothane (0.5–1.0 per cent). Ventilation was adjusted to maintain normocapnia and end tidal CO_2 was monitored by a Datex infra-red CO_2 analyzer.

The ulnar nerve was stimulated percutaneously at the elbow with square wave supramaximal stimuli of 0.2 ms duration, delivered in a train-of-four (TOF) sequence at 2 Hz frequency every ten seconds, using a Myotest peripheral nerve stimulator (Biometer). The resultant contraction of adductor pollicis was recorded using a force displacement transducer and neuromuscular function analyzer (Myograph 2000, Biometer).[10] The preload tension on the thumb was maintained at 300 g throughout the investigation.

After stabilization of twitch recording, atracurium 0.5 $mg \cdot kg^{-1}$ was administered and tracheal intubation was performed at maximum block. Atracurium 0.5 $mg \cdot kg^{-1}$ was the only dose given during the procedures.

At the end of surgery, when spontaneous neuromuscular recovery had begun and the first twitch (T_1) of the TOF had returned to ten per cent of the control value, patients were randomly allocated to two groups. In Group I, neostigmine 0.05 $mg \cdot kg^{-1}$ was administered in a single bolus dose preceded by 0.02 $mg \cdot kg^{-1}$ atropine. In Group II an initial dose of neostigmine 0.01 $mg \cdot kg^{-1}$ was administered followed three minutes later by 0.04 $mg \cdot kg^{-1}$. In the latter group, 0.5 mg atropine was administered before the injection of the first dose of neostigmine and the remainder of the dose was administered before the second dose of neostigmine. The same total dose of neostigmine 0.05 $mg \cdot kg^{-1}$ and atropine 0.02 $mg \cdot kg^{-1}$ were administered to all patients.

Patients continued to receive 70 per cent nitrous oxide in oxygen and 0.5–1 per cent halothane until all measurements were complete. Antagonism of block was considered adequate when a TOF ratio (the amplitude of the fourth to the first evoked response; T_4/T_1) of 0.75 was attained.[11]

The following parameters were calculated: (a) T_1 and TOF ratio in Group I, three minutes after the administration of neostigmine 0.05 $mg \cdot kg^{-1}$; (b) T_1 and TOF ratio in Group II, three minutes after the administration of the initial dose of neostigmine 0.01 $mg \cdot kg^{-1}$ (just before the administration of the second dose); (c) times taken for the twitch height (T_1) to recover from 25 to 75 per cent of control and from 75 to 100 per cent of control; (d) time taken from the first injection of the drug until the TOF ratio value had reached 0.75; (e) times taken for TOF ratio of 0.25 to TOF ratio of 0.5 and 0.75; and (f) the TOF ratio at ten per cent increments of T_1 tension recovery.

Data analysis

The results in the two groups were compared using an unpaired Student's t-test.

The mean values of every other TOF ratio, starting three minutes from the first injection of neostigmine, were calculated for the 16 patients in each group and were utilized for linear regression analysis. Twenty-two pairs of observations were used to obtain the regression equations. The independent and dependent variables, respectively, were time and TOF ratio. Regression lines were constructed using the method of least squares. The slopes of the regression lines were compared using analysis of covariance. A p value <0.05 was considered statistically significant.

Results

All results are expressed as mean $\pm$SD. There was no significant difference between the groups regarding the patients' age or weight (Table I). Times from the injection of atracurium to ten per cent recovery of the first twitch (T_1) of TOF were 36.3 ± 5.4 and 35.9 ± 4.8 minutes in Groups I and II respectively.

Three minutes after the administration of neostigmine 0.01 $mg \cdot kg^{-1}$ in Group II (just before the administration of the second dose of neostigmine), the height of T_1 and the TOF ratio were 44 per cent and 0.17 respectively. In contrast, there was a significant ($p < 0.001$) acceleration of recovery of

TABLE I Demographic data

		Age (years)	*Weight (kg)*	*Sex (M/F)*
Group I (n = 16)	Single dose	26.6 ± 7.4	61.9 ± 8	7/9
Group II (n = 16)	Divided dose	27.5 ± 9.7	63.5 ± 7	8/8

TABLE II First twitch (T_1) and train-of-four (TOF) ratio 3 minutes from the first administration of neostigmine

		T_1 (% of control)	*TOF ratio*
Group I (n = 16)	Single dose	78.75 ± 17	0.45 ± 0.1
Group II (n = 16)	Divided dose	44.06 ± 10.03	0.17 ± 0.1
p		<0.001	<0.001

TABLE III Recovery of the first twitch in the train-of-four (T_1)

		Time for T_1 recovery (seconds)	
		from 25%–75% of control	*from 75%–100% of control*
Group I (n = 16)	Single dose	110.3 ± 49.7	94 ± 40.1
Group II (n = 16)	Divided dose	152.8 ± 32.9	70.6 ± 29.5
p		<0.005	<0.05

T_1 and TOF ratio (78.7 per cent and 0.45 respectively) three minutes after the administration of neostigmine 0.05 mg·kg^{-1} in Group I (Table II). This indicates the relative ineffectiveness of the initial dose of neostigmine administered in Group II.

The time taken for the twitch height (T_1) to recover from 25 to 75 per cent of the control value was significantly shorter ($p < 0.005$) in Group I. In contrast, the recovery time of T_1 from 75 to 100 per cent of control was significantly faster ($p < 0.05$) in Group II (Table III).

Administration in divided doses resulted in a significantly faster recovery of the TOF ratios as assessed by times taken for the TOF ratio of 0.25 to recover to one of 0.5 and 0.75 as shown in Figure 1 and Table IV. In Group II, the time from the first

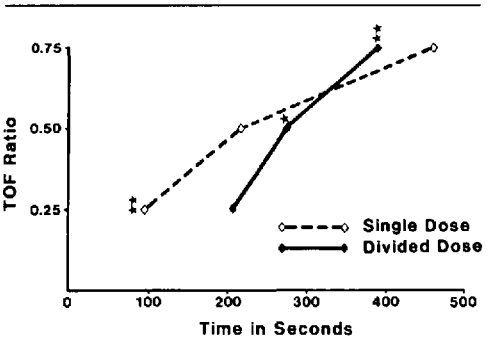

FIGURE 1 Recovery of the train-of-four ratio after neostigmine administration in single (n = 16) or divided doses (n = 16). Times for TOF ratio recovery from 0.25 to 0.5 and from 0.5 to 0.75 were significantly faster after neostigmine administration in divided doses.
*p < 0.005
*p < 0.001

injection of neostigmine until the TOF ratio value had reached 0.75 was 391.8 ± 83.3 seconds. This was significantly shorter ($p < 0.05$) when compared to 468.6 ± 150.3 seconds in Group I.

The equation of the regression line in Group I was

$$y = 0.430003 + 0.000577x \qquad (r = 0.57)$$

and for Group II was

$$y = 0.115418 + 0.001483x \qquad (r = 0.66)$$

where "y" corresponds to TOF ratio, "x" to the time and "r" is the correlation coefficient. The slope of the regression line in Group II is 2.5 times that in Group I. This indicates that the rate of TOF ratio recovery following administration in divided doses was 2.5 times faster than that following single bolus administration. Analysis of covariance yielded a significant difference ($p < 0.01$) between the slopes of the regression lines in both groups.

TABLE IV Recovery of the train-of-four (TOF) ratio

		Time for TOF ratio recovery (seconds)		
		from 0.25 to 0.5	*from 0.5 to 0.75*	*from 0.25 to 0.75*
Group I (n = 16)	Single dose	118.9 ± 43.9	240.1 ± 116	365.3 ± 139.8
Group II (n = 16)	Divided Dose	73.5 ± 21.9	112.6 ± 41.8	186.2 ± 54.6
p		<0.005	<0.001	<0.001

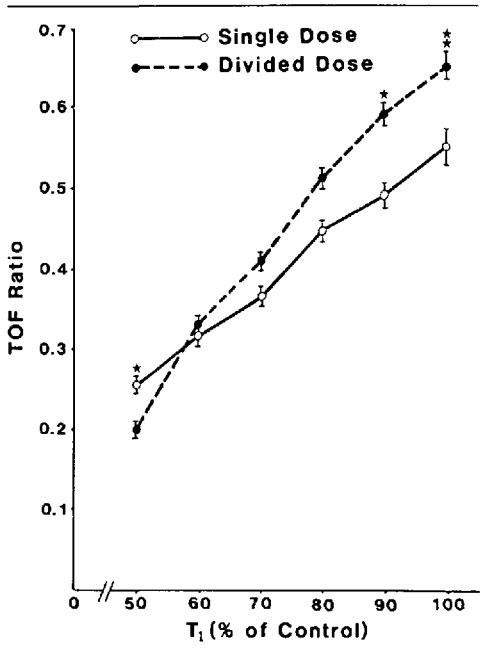

FIGURE 2 Relationship of train-of-four (TOF) and first twitch tension during antagonism of block after administration of neostigmine in single (n = 16) or divided doses (n = 16).
*$p < 0.05$
‡$p < 0.025$

The mean values of the TOF ratios for ten per cent increments of T_1 tension are shown for each group in Figure 2. The TOF ratios during antagonism were significantly higher after divided doses at T_1 twitch heights ranging from 90 to 100 per cent.

Discussion

The acetylcholinesterase responsible for the rapid hydrolysis of acetylcholine at the neuromuscular junction is a membrane-bound enzyme located at both presynaptic and postsynaptic membranes.* It is best viewed as having two subunits, the anionic site and the esteratic site.[12] The anionic site is responsible for the high substrate specificity as well as promoting (accelerating) activity at the esteratic site.[13] The esteratic site is of low specificity and is responsible for the hydrolytic process.[13] The principal mechanism of action of anticholinesterase is by inhibiting the hydrolysis of aceylcholine, thereby allowing accumulation of acetylcholine at the receptor site.[14] Neostigmine contains a carbamate group which is transferred and chemically bonded to the esteratic subunit on acetylcholinesterase. Once this occurs, the enzyme is inhibited and acetylcholine reaches such a level that it preferentially occupies the cholinergic receptors and prevents access of the non-depolarizing neuromuscular blocking agent. Direct stimulation of the end-plate region[16] and direct facilitatory effect at the presynaptic motor nerve ending[17] have also been found to contribute to the anticurare action of neostigmine.

Basta *et al.*[18] reported that during atracurium blockade the recovery of first twitch in the TOF from 15 to 95 per cent of control was achieved after 10.5 minutes (630 seconds) following 0.06 $mg \cdot kg^{-1}$ neostigmine. At a 20 per cent spontaneous recovery of the twitch height following atracurium blockade, Baird and Kerr[19] administered 0.75 $mg \cdot kg^{-1}$ edrophonium. They found that the TOF ratio of 0.75 was achieved after 6.6 minutes (396 seconds). Several studies have demonstrated that edrophonium has a more rapid onset of action and shorter duration to peak effects as compared to neostigmine.[20,21,22] In this study, administration of neostigmine in divided doses at a deeper level of block (ten per cent recovery of twitch height) resulted in an accelerated rate of recovery of neuromuscular blockade. The time taken to attain a TOF ratio of 0.75 was 391 seconds. This indicated that administration of neostigmine in divided doses accelerated the reversal of neuromuscular blockade in a time comparable to using an equipotent dose of edrophonium.

The time taken for T_1 to recover from 25 to 75 per cent of the control value was shorter in Group I. This can probably be attributed to difference in the method of drug administration in both groups. The initial small dose of neostigmine administered to Group II was not of enough magnitude to accelerate the recovery of T_1 to that seen in Group I (Table II). However, the rate of recovery of neuromuscular function was faster after the administration of the second dose of neostigmine in Group II as evidenced by the steeper slope of the regression line. This acceleration resulted in a significant ($p < 0.05$) shorter recovery time of the T_1 from 75 to 100 per cent of the control (Table III) as well as shorter

*Sokoll MD, Gergis SD. Neuromuscular transmission: anatomy, physiology and pharmacology. ASA Refresher Courses in Anesthesiology 1977; 5: 179–90.

times ($p < 0.005$ and $p < 0.001$) for the TOF ratios to recover from 0.25 to 0.5 and 0.75 (Table IV and Figure 1).

This phenomenon has not been demonstrated before, but it may be explained on the basis of a recent work[23] on the kinetics of erythrocyte cholinesterase, the properties of which are very similar to neuromuscular junction cholinesterase.[24] Facilitation of twitch height did not occur when erythrocyte cholinesterase was inhibited less than 85 per cent. Between 85 and 98 per cent inhibition, facilitation was linearly related to enzyme inhibition.[23] Therefore, a large proportion of the acetylcholinesterase could be inhibited without effect on neuromuscular function.[15] This suggests a "margin of safety" in enzyme inhibition[25] similar to that seen during blockade of neuromuscular transmission by non-depolarizing muscle relaxants.[26] By analogy to the priming principle,[27] the initial relatively ineffective dose of neostigmine will cause partial enzyme inhibition and therefore will decrease the "margin of safety" of acetylcholinesterase enzyme, allowing a more pronounced effect of the second dose.

Bowman[28] suggested that depression of T_1 and the TOF fade are independent effects of acetylcholine antagonists; the former is the result of postjunctional block whereas the latter arise from the action of prejunctional receptors. In the present study, the relationship between TOF fade and first twitch depression antagonist properties was examined. The TOF ratios during antagonism were significantly higher after divided doses at T_1 twitch heights ranging from 90 to 100 per cent of control (Figure 2). It might be speculated that this prejunctional activity was responsible for the accelerated recovery of the TOF ratios observed after administration of neostigmine in divided doses.

In clinical practice the ability to accelerate the reversal of non-depolarizing neuromuscular blockade would be advantageous. However, further studies will be required in order to define precisely the size of the initial dose, the optimal time interval between the doses and possibly the optimal combination of different anticholinesterases.

In conclusion, administration of neostigmine 0.04 $mg \cdot kg^{-1}$ three minutes after an initial dose of 0.01 $mg \cdot kg^{-1}$ of the drug produced a significantly more rapid reversal of residual atracurium-induced neuromuscular blockade as compared to a single bolus administration.

Acknowledgments

We wish to thank Mr. A. Halim Kamel and Mr. A.S. Archibald from the Medical Illustrations Department for their help, and Ms Paz Raynoso for typing the manuscript.

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Résumé

L'hypothèse que l'administration de néostigmine à doses divisées peut accélérer l'antagonisme du block neuromusculaire était investiguée. La néostigmine 0.05 mg·kg^{-1} était administrée soit en bolus unique (Group I, n = 16) ou en une dose initiale de 0.01 mg·kg^{-1} suivi trois minutes plus tard de 0.04 mg·kg^{-1} (Group II, n = 16) pour l'antagonisme d'un block induit par l'atracurium. Le renversement du block était tenté lorsqu'on a observé le recouvrement spontané de dix pour cent dans la hauteur de twitch. Le temps moyen (±SD) à partir de la première injection du médicament jusqu'à l'obtention d'une ondée de quatre (TOF) de 75 pour cent était significativement plus cour dans le groupe II ($p < 0.05$) que dans le Groupe I (391.8 ± 83.3 et 468.6 ± 150.3 secondes respectivement). Le taux de recouvrement de l'ondée de quatre (TOF) était 2.5 fois plus rapide après l'administration de néostigmine à dose divisée.

On conclue que l'administration de néostigmine à doses divisées, telle que décrites dans cette étude, produit un antagonisme significativement plus rapide du block neuromusculaire induit par l'atracurium comparativement à l'administration de la néostigmine en un bolus unique.