Neostigmine and edrophonium for reversal of pipecuronium neuromuscular blockade

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Neostigmine $0.06 \text{ mg} \cdot \text{kg}^{-1}$ or edrophonium $1 \text{ mg} \cdot \text{kg}^{-1}$ were administered to two groups of 15 patients each for antagonism of pipecuronium-induced neuromuscular block at 20% spontaneous recovery of the first twitch (T_1) of the train-of-four (TOF) stimulation. The mean onset of action ($\pm \text{SEM}$) of edrophonium ($18.1 \pm 2.4 \text{ sec}$) was significantly more rapid ($P < 0.01$) than that of neostigmine ($47.6 \pm 4 \text{ sec}$), as were the times taken to attain a TOF ratio of 0.25 and 0.5. Nevertheless, the reversal time (time taken from the end of injection of the antagonist until TOF ratio value had reached 0.75) was significantly shorter ($P < 0.01$) in the neostigmine than in the edrophonium group (499.3 ± 62 vs $767 \pm 52 \text{ sec}$ respectively). The TOF ratio ten minutes after reversal was greater in the neostigmine group than in the edrophonium group ($P < 0.01$), 0.78 ± 0.02 vs 0.68 ± 0.02 min respectively. At that time, 33% (5 out of 15) and 80% (12 out of 15) patients failed to be reversed adequately (TOF ratio of 0.75) after neostigmine $0.06 \text{ mg} \cdot \text{kg}^{-1}$ and edrophonium $1 \text{ mg} \cdot \text{kg}^{-1}$, respectively. Administration of one additional dose (one-third of the initial dose) of the same antagonist resulted in adequate antagonism in the remaining five patients in the neostigmine group and in nine patients in the edrophonium group. Two such doses were required in the remaining three patients in the latter group. The mean total dose of neostigmine and edrophonium employed in this study was 0.067 ± 0.002 and $1.3 \pm 0.05 \text{ mg} \cdot \text{kg}^{-1}$, respectively. Under the conditions of this study, edrophonium in

a dose of $1 \text{ mg} \cdot \text{kg}^{-1}$ did not consistently antagonize residual neuromuscular blockade induced by pipecuronium at 20% recovery of T_1 .

La néostigmine $0.06 \text{ mg} \cdot \text{kg}^{-1}$ ou l'édrophonium $1 \text{ mg} \cdot \text{kg}^{-1}$ ont été administrés à deux groupes de 15 patients chaque pour antagoniser le bloc neuromusculaire induit par le pipécuronium à 20% de récupération spontanée du premier twitch (T_1) de l'ondée-de-quatre (TOF). Le temps d'installation moyen de l'action ($\pm \text{SEM}$) de l'édrophonium ($18.1 \pm 2.4 \text{ sec}$) était significativement plus rapide ($P < 0.01$) que celui de la néostigmine ($47.6 \pm 4 \text{ sec}$), et il en était de même pour les temps pris pour obtenir un ratio de TOF de 0.25 et 0.5. Néanmoins, le temps d'antagonisme (temps à partir de la fin de l'injection de l'antagonisme jusqu'à un ratio de TOF de 0.75) était significativement plus court ($P < 0.01$) dans le groupe néostigmine que dans le groupe édrophonium (499.3 ± 62 vs $767 \pm 52 \text{ sec}$ respectivement). Le ratio TOF dix minutes après l'antagonisme était significativement plus grand dans le groupe néostigmine que dans le groupe édrophonium ($P < 0.01$), étant de 0.78 ± 0.02 vs 0.68 ± 0.02 min respectivement. A ce moment-là, 33% (5 sur 15) et 80% (12 sur 15) patients n'ont pas démontré un antagonisme adéquat (TOF ratio de 0.75) après néostigmine $0.06 \text{ mg} \cdot \text{kg}^{-1}$ et édrophonium $1 \text{ mg} \cdot \text{kg}^{-1}$ respectivement. L'administration d'une dose additionnelle (1/3 de la dose initiale) du même antagoniste a amené un antagonisme adéquat chez les cinq autres patients dans le groupe néostigmine et chez neuf autres patients dans le groupe édrophonium. Deux autres doses ont été nécessaires pour les trois autres patients du dernier groupe. La dose totale moyenne de néostigmine et d'édrophonium employée dans cette étude était de 0.067 ± 0.002 et $1.3 \pm 0.05 \text{ mg} \cdot \text{kg}^{-1}$ respectivement. Sous les conditions de cette étude, l'édrophonium à des doses de $1 \text{ mg} \cdot \text{kg}^{-1}$ n'a pas toujours antagonisé le bloc neuromusculaire résiduel induit par la pipécuronium à 20% de récupération de T_1 .

Key words

ANTAGONISTS, NEUROMUSCULAR RELAXANTS,

edrophonium, neostigmine;

NEUROMUSCULAR RELAXANTS: pipecuronium;

NEUROMUSCULAR TRANSMISSION: train-of-four.

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Neostigmine is the most commonly used antagonist for the reversal of the residual effects of nondepolarizing muscle relaxants. It is now accepted, however, that

edrophonium in doses of $0.5\text{--}1.5\text{ mg}\cdot\text{kg}^{-1}$ can effectively antagonize a nondepolarizing neuromuscular block.¹⁻³

Pipecuronium bromide is a new long-acting, nondepolarizing muscle relaxant which is devoid of cardiovascular effects.⁴ Wierda *et al.*⁵ noted the variability in response to edrophonium $0.5\text{--}0.75\text{ mg}\cdot\text{kg}^{-1}$ during the reversal of residual pipecuronium-induced neuromuscular blockade.

This study was designed to examine the effectiveness of neostigmine $0.06\text{ mg}\cdot\text{kg}^{-1}$ and edrophonium $1\text{ mg}\cdot\text{kg}^{-1}$ administered at the same degree of spontaneous recovery in reversing the action of a single bolus dose of pipecuronium. These doses were documented previously to be equipotent in the reversal of pancuronium neuromuscular block.⁶

Methods

After institutional approval, 30 ASA physical status I or II adult patients of either sex were studied. All patients were undergoing elective procedures, were free of neuromuscular, renal or hepatic disease and were not taking any drug known to interfere with neuromuscular function. Informed consent was obtained. All patients received 10–15 mg diazepam po 90 min preoperatively.

An iv infusion of lactated Ringer's solution was established prior to induction of anaesthesia. The ECG and nasopharyngeal temperatures were monitored continuously. Body temperature varied less than 0.5°C throughout the studies. Blood pressure was measured every five minutes by an electronic oscillometer (Dinamap, Critikon, Inc., Tampa, USA).

In all patients, anaesthesia was induced with fentanyl $2\text{ }\mu\text{g}\cdot\text{kg}^{-1}$, thiopentone $5\text{ mg}\cdot\text{kg}^{-1}$, and was maintained with 70% nitrous oxide in oxygen and halothane (0.5–1%). Inspired halothane concentration and end-tidal CO_2 were monitored by a Datex Capnomac monitor (Datex Instrumentarium, Helsinki, Finland). Ventilation was adjusted to maintain normocapnia (PETCO_2 35–40 mmHg).

The ulnar nerve was stimulated at the wrist with square wave supramaximal stimuli of 0.2 ms duration, delivered in a train-of-four (TOF) sequence at 2 Hz every ten seconds, using a Myotest peripheral nerve stimulator (Biometer International, Odense, Denmark). The resultant contraction of the adductor pollicis was recorded using a force displacement transducer and neuromuscular function analyzer (Myograph 2000, Biometer International, Odense, Denmark).⁷ Preload tension on the thumb was maintained at 300 g throughout the investigation.

After stabilization of the twitch recording, pipecuronium $70\text{ }\mu\text{g}\cdot\text{kg}^{-1}$ was administered and tracheal intubation was performed at maximum block. Patients were excluded from the study if additional doses of pipecuronium were given.

At the end of surgery, when spontaneous recovery had

begun and the first twitch (T_1) of the TOF had returned to 20% of the control value, patients were randomly allocated to two groups ($n = 15$ in each) to receive either neostigmine $0.06\text{ mg}\cdot\text{kg}^{-1}$ (Group I) or edrophonium $1\text{ mg}\cdot\text{kg}^{-1}$ (Group II) in a mixture with atropine.

Patients continued to receive 70% nitrous oxide in oxygen and 0.5–1% 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.⁸ Additional doses of the same reversal agent (one-third of the first dose) were given at 10 and 15 min if the TOF ratio had not reached 0.75. Further assessment of the patients was carried out in the Recovery Room for 60 min using clinical criteria such as the ability to open eyes, cough and sustain a head lift.

The following variables were calculated:

- a Time from the end of injection of pipecuronium to 20% recovery of T_1 (Clinical duration);
- b Time from injection of the antagonist until first increase of the twitch was observed (onset time);
- c Time for twitch height (T_1) to recover from 25 to 75% of control (recovery index);
- d Times to attain TOF ratios of 0.25, 0.5 and 0.75;
- e TOF ratio at ten minutes; and
- f The TOF ratio at 20% increments of T_1 tension recovery.

Statistical analyses were carried out with Student's *t* test and Mann-Whitney test where applicable using BMDP (1988) statistical package (University of California Press).

Results

Results are expressed as means $\pm$ SEM. There was no significant difference between the groups regarding the patients' age or weight. The mean age and body weight were 30.3 ± 2.3 yr and 63.1 ± 2.6 kg and 30 ± 1.9 yr and 63 ± 2.7 kg in Groups I and II, respectively.

The clinical duration of the $70\text{ }\mu\text{g}\cdot\text{kg}^{-1}$ dose of pipecuronium was 58.4 ± 4.1 , and 61.1 ± 3.6 min in Groups I and II, respectively.

The mean onset time following the administration of edrophonium $1\text{ mg}\cdot\text{kg}^{-1}$ was 18.1 ± 2.4 sec. This was shorter ($P < 0.0001$) than the 47.6 ± 4 sec in those patients receiving neostigmine $0.06\text{ mg}\cdot\text{kg}^{-1}$. The time taken for the twitch height (T_1) to recover from 25 to 75% of the control value (recovery index) was significantly shorter in Group II (Table). Similarly, the times required to attain TOF ratios of 0.25 and 0.50 were less ($P < 0.01$) in those receiving edrophonium (Table). Although the initial rate of recovery of edrophonium group was greater, TOF ratio ten minutes after reversal was greater in the neostigmine group than in the edrophonium group; 0.78 ± 0.02 vs 0.68 ± 0.02 , respectively ($P < 0.01$).

FIGURE 1 TOF ratios in individual patients ten minutes after administration of neostigmine $0.06 \text{ mg} \cdot \text{kg}^{-1}$ or edrophonium $1.0 \text{ mg} \cdot \text{kg}^{-1}$. (—) Indicates the mean for the groups. Circles represent individual patients. *Indicates significant difference ($P < 0.01$).

In contrast to neostigmine $0.06 \text{ mg} \cdot \text{kg}^{-1}$ where the TOF recovery reached 0.75 or more in ten patients (67%) at ten minutes post-reversal, the same degree of reversal after edrophonium $1 \text{ mg} \cdot \text{kg}^{-1}$ was reached only in three patients (20%) (Figure 1).

Administration of one additional dose (one-third of the initial dose) of the same antagonist resulted in adequate antagonism (TOF of 0.75) in the remaining five patients in the neostigmine group and in nine patients in the edrophonium group. Two such doses were required in the remaining three patients in edrophonium group. The mean total doses of neostigmine and edrophonium employed in this study were 0.067 ± 0.002 and $1.3 \pm 0.05 \text{ mg} \cdot \text{kg}^{-1}$, respectively.

Although recovery after edrophonium was more rapid

FIGURE 2 Relationship of train-of-four (TOF) ratio and first twitch tension (T_1) during the antagonism of residual pipecuronium blockade after administration of neostigmine and edrophonium. The data shown is mean TOF ratio $\pm$ SEM at each point. * $P < 0.05$.

initially than after neostigmine, reversal time (time to attain a TOF ratio of 0.75) was shorter in the neostigmine group ($P < 0.01$) (Table).

The mean values of TOF ratio for 20% increments of T_1 are shown for each antagonist in Figure 2. There were no statistically significant differences in TOF ratio recovery between the antagonists when $T_1 < 100\%$ of control. However, at $T_1 = 100\%$ of control, the TOF ratio was greater ($P < 0.05$) with neostigmine than with edrophonium (Figure 2).

Discussion

Pipecuronium is a new long-acting bisquaternary nondepolarizing neuromuscular blocking agent with a chemical structure similar to that of pancuronium.⁹ Boros *et al.*¹⁰ noted that the neostigmine requirements to antagonize the residual neuromuscular blockade were similar for both

TABLE Onset time, recovery index, times to attain different TOF ratios and TOF ratio at ten minutes. Mean $\pm$ SEM

	Onset time* (sec)	Recovery† index (sec)	Times (sec) to attain TOF ratio of			TOF ratio at 10 minutes	Dose $\text{mg} \cdot \text{kg}^{-1}$
			0.25	0.50	0.75		
Group I ($n = 15$) Neostigmine	47.6 ± 4	191.6 ± 22	98.6 ± 10	222 ± 31	499.3 ± 62	0.78 ± 0.02	0.067 ± 0.002
Group II ($n = 15$) Edrophonium	18.1 ± 2.4	63.8 ± 6.4	33.6 ± 3.3	99 ± 16.5	767.6 ± 52	0.68 ± 0.02	1.3 ± 0.005
P	<0.0001	$=0.0001$	<0.0001	<0.01	<0.01	<0.01	

*Onset time, was the time from the injection of the antagonist until first increase of the twitch was observed.

†Recovery index, was the time for the twitch heights (T_1) to recover from 25 to 75 per cent of control.

pancuronium and pipecuronium. In adults, pipecuronium is approximately 20% more potent than pancuronium with an ED₉₅ of approximately 47 $\mu\text{g} \cdot \text{kg}^{-1}$ during halothane anaesthesia.⁵

Edrophonium antagonism of neuromuscular blockades induced by pancuronium, atracurium and vecuronium has been extensively studied.^{1-3,6,11-18} In nine of these studies, edrophonium was compared directly with neostigmine.^{1,3,6,13-18} From all studies one can conclude that for antagonism of neuromuscular blockade when T₁ is 10% of control twitch tension or less, the dose of edrophonium should be 1–1.5 $\text{mg} \cdot \text{kg}^{-1}$ to be as rapid as neostigmine 0.04 $\text{mg} \cdot \text{kg}^{-1}$. Nevertheless, Donati *et al.*¹⁹ noted that the effect of the reversal agents is dependent on the relaxants, so that reversal of atracurium or vecuronium would be faster than that of pancuronium or d-tubocurarine. The dose of neostigmine required to reverse neuromuscular blockade was less after a bolus dose of vecuronium than pancuronium.²⁰

This study has shown that neostigmine and edrophonium reverse the action of pipecuronium at different rates. Edrophonium 1 $\text{mg} \cdot \text{kg}^{-1}$ was more rapid in onset than neostigmine 0.06 $\text{mg} \cdot \text{kg}^{-1}$. Antagonism following edrophonium proceeded at a significantly more rapid rate until TOF ratio value had reached 0.5. In contrast, TOF ratio at ten minutes was greater ($P < 0.01$) following neostigmine than edrophonium. Similarly, mean time to reach a TOF ratio of 0.75 was 499.3 ± 62 sec (8.3 min) with neostigmine compared with 767.6 ± 52 sec (12.7 min) with edrophonium. Similar findings of inadequate antagonism following pipecuronium have been reported by Wierda *et al.*⁵ when edrophonium 0.5 $\text{mg} \cdot \text{kg}^{-1}$ was administered at spontaneous recovery of T₁ to 25% of control value. They also noted that a supplemental dose (half of the initial dose) injected ten minutes after reversal resulted in only a marginal improvement in the TOF recovery and concluded that edrophonium was a less safe antagonist of pipecuronium than neostigmine.⁵ However, the increase in the TOF ratio after the supplemental doses of edrophonium, as observed in this study, suggests the beneficial effects of still higher doses up to 1.6 $\text{mg} \cdot \text{kg}^{-1}$ of edrophonium. Nevertheless, our observations also indicate that the effect of edrophonium was associated with more variability than that of neostigmine. The doses of neostigmine and edrophonium employed in this study were equipotent when used for antagonism of pancuronium blockade.⁶ Our results indicate, however, that neostigmine 0.06 $\text{mg} \cdot \text{kg}^{-1}$ was more potent than edrophonium 1 $\text{mg} \cdot \text{kg}^{-1}$ in reversing the residual neuromuscular blockade induced by pipecuronium. It has been noted that the neostigmine:edrophonium potency ratio is dependent on the relaxant used,¹⁸ and this could explain our results.

Graham *et al.*²¹ found that twitch depression and TOF ratio bear a fixed relation in time and, on the basis of a kinetic model, concluded that different rate constants indicate separate sites of action. In the present study, the relationship between TOF fade and first twitch depression was examined. The TOF ratios during antagonism were not significantly different between the two groups at T₁ twitch heights less than 100% of control (Figure 2). However, at 100% recovery of T₁, TOF ratios were significantly greater in neostigmine group. This seems to contradict the prediction made from TOF analysis in previous studies,^{13,22} where it was observed that edrophonium had a greater ability to reverse fade. Donati *et al.*¹⁹ noted that edrophonium was less capable of reversing fade than first twitch. In accordance with our results, the same group reported that the fade-reversing effect of edrophonium was observed only when the reversal was incomplete.^{19,22} The fade-reversing properties of edrophonium were observed at low doses, and this comparative advantage was lost at higher doses,¹⁹ as those employed in our study. Neostigmine was found to be more effective in reversing a TOF response previously depressed by vecuronium than atracurium.¹⁸ This supports the concept that the reversal characteristics of an antagonist might depend on which relaxant was used to produce neuromuscular block.

We conclude that when reversal was attempted at 20% recovery after a single bolus dose of pipecuronium, neostigmine was more reliable than edrophonium. Although the initial recovery was more rapid after edrophonium, at ten minutes after reversal 80% (12 out of 15) and 33% (5 out of 15) patients failed to be adequately recovered (TOF ratio of 0.75) after edrophonium 1 $\text{mg} \cdot \text{kg}^{-1}$ and neostigmine 0.06 $\text{mg} \cdot \text{kg}^{-1}$ respectively. Administration of an additional dose (one-third of the initial dose) of the same antagonist resulted in adequate antagonism in the remaining patients in the neostigmine group and in nine patients in the edrophonium group. Under the conditions of this study, it appears prudent to administer relatively high doses of neostigmine or edrophonium when pipecuronium has been given.

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References

- 1 Ferguson A, Egerszegi P, Bevan DR. Neostigmine, pyridostigmine, and edrophonium as antagonists of pancuronium. *Anesthesiology* 1980; 53: 390–4.
- 2 Naguib M, Abdulatif M, Absood GH. Accelerated reversal of atracurium blockade with priming doses of edrophonium. *Anesthesiology* 1987; 66: 397–400.
- 3 Engbaek J, Ording H, Ostergaard D, Viby-Mogensen J. Edrophonium and neostigmine for reversal of the neuromuscular blocking effect of vecuronium. *Acta Anaesthesiol Scand* 1985; 29: 544–6.
- 4 Boros M, Szenohradszky J, Kertesz A, Marosi GY, Tutsek L. Clinical experiences with pipecuronium bromide. *Acta Chir Hung* 1983; 24: 207–14.
- 5 Wierda JMKH, Richardson FJ, Agoston S. Dose-response relation and time course of action of pipecuronium bromide in humans anesthetized with nitrous oxide and isoflurane, halothane, or droperidol and fentanyl. *Anesth Analg* 1989; 68: 208–13.
- 6 Breen PJ, Doherty WG, Donati F, Bevan DR. The potencies of edrophonium and neostigmine as antagonists of pancuronium. *Anaesthesia* 1985; 40: 844–7.
- 7 Viby-Mogensen J. Clinical evaluation of neuromuscular transmission. *Br J Anaesth* 1982; 54: 209–23.
- 8 Ali HH, Kitz RJ. Evaluation of recovery from non-depolarizing neuromuscular block using a digital neuromuscular transmission analyzer: preliminary report. *Anesth Analg* 1973; 52: 740–3.
- 9 Karpati E, Biro K. Pharmacological study of a new competitive neuromuscular blocking steroid, pipecurium bromide. *Arzneimittelforschung* 1980; 30: 346–54.
- 10 Boros M, Szenohradszky J, Marsoi Y, Toth I. Comparative clinical study of pipecurium bromide and pancuronium bromide. *Arzneimittelforschung* 1980; 30: 389–93.
- 11 Bevan DR. Reversal of pancuronium with edrophonium. *Anaesthesia* 1979; 34: 614–9.
- 12 Cronnelly R, Morris RB, Miller RD. Edrophonium: duration of action and atropine requirement in humans during halothane anesthesia. *Anesthesiology* 1982; 57: 261–6.
- 13 Lavery GG, Mirakhur RJ, Gibson FM. A comparison of edrophonium and neostigmine for the antagonism of atracurium-induced neuromuscular block. *Anesth Analg* 1985; 64: 867–70.
- 14 Rupp SM, McChristian JW, Miller RD, Taboada JA, Cronnelly R. Neostigmine and edrophonium antagonism of varying intensity neuromuscular blockade induced by atracurium, pancuronium or vecuronium. *Anesthesiology* 1986; 64: 711–7.
- 15 Sanfilippo M, Vilardi V, Fierro G, Rosa G, Pelaia P, Gasparetto A. Neostigmine and edrophonium as antagonists of atracurium and pancuronium. *Acta Anaesthesiol Scand* 1988; 32: 437–40.
- 16 Astley BA, Hughes R, Payne JP. Antagonism of atracurium-induced neuromuscular blockade by neostigmine or edrophonium. *Br J Anaesth* 1986; 58: 1290–5.
- 17 Jones RM, Pearce AC, Williams JP. Recovery characteristics following antagonism of atracurium with neostigmine or edrophonium. *Br J Anaesth* 1984; 56: 453–7.
- 18 Smith CE, Donati F, Bevan DR. Dose-response relationships for edrophonium and neostigmine as antagonists of atracurium and vecuronium neuromuscular blockade. *Anesthesiology* 1989; 71: 37–43.
- 19 Donati F, McCarroll SM, Antzaka C, McCready D, Bevan DR. Dose-response curves for edrophonium, neostigmine, and pyridostigmine after pancuronium and d-tubocurarine. *Anesthesiology* 1987; 66: 471–6.
- 20 Fahey MR, Morris RB, Miller RD, Sohn YJ, Cronnelly R. Clinical pharmacology of ORG NC45 (Norcuron TM): a new nondepolarizing muscle relaxant. *Anesthesiology* 1981; 55: 6–11.
- 21 Graham GG, Morris R, Pybus DA, Torda TA, Woodey R. Relationship of train-of-four ratio to twitch depression during pancuronium-induced neuromuscular blockade. *Anesthesiology* 1986; 65: 579–83.
- 22 Donati F, Ferguson A, Bevan DR. Twitch depression and train-of-four ration after antagonism of pancuronium with edrophonium, neostigmine, or pyridostigmine. *Anesth Analg* 1983; 62: 314–6.