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Enzymatic Versus Pharmacologic Antagonism of Profound Mivacurium-induced Neuromuscular Blockade

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Background: Mivacurium, a nondepolarizing muscle relaxant, is hydrolyzed by butyrylcholinesterase. The use of butyrylcholinesterase for antagonism of profound mivacurium-induced blockade has not been studied in humans. In part 1 of this two-part study, the authors examined the relationship between the posttetanic count (PTC) and recovery from profound mivacurium-induced blockade. In part 2, an attempt was made to antagonize a quantified level of profound mivacurium-induced blockade using either butyrylcholinesterase, edrophonium, or neostigmine.

Methods: Eighty-seven ASA physical status 1 or 2 adult patients were given $0.15 \text{ mg} \cdot \text{kg}^{-1}$ mivacurium during fentanyl-thiopental-nitrous oxide-isoflurane anesthesia. They were randomly assigned to eight groups. Neuromuscular function was monitored by recording the mechanomyographic response of the adductor pollicis to PTC and train-of-four (TOF) stimulation in all patients except those in group 1 where the TOF was the only pattern used. In part 1, neuromuscular function was allowed to recover spontaneously in ten patients (group 1; control-TOF) until TOF ratio (the amplitude of the fourth evoked response as a fraction of the first evoked response: T_4/T_1) had reached 0.75. The temporal relationship between PTC and the first reaction to TOF stimulation was determined in another 21 patients, and neuromuscular function in 10 of these patients was allowed to recover spontaneously until TOF ratio had reached 0.75 (group 2; control-

PTC). In part 2, the antagonism of mivacurium-induced profound (PTC ≥ 1 ; groups 3-6) and 90% block (groups 7-8) of twitch height were investigated in another 56 patients. Groups 3 and 7 received neostigmine $0.06 \text{ mg} \cdot \text{kg}^{-1}$ whereas groups 4 and 8 received edrophonium $1 \text{ mg} \cdot \text{kg}^{-1}$, respectively. Groups 5 and 6 received exogenous human butyrylcholinesterase equivalent to activity present in 25 or 70 $\text{ml} \cdot \text{kg}^{-1}$ of human plasma, respectively.

Results: Neither butyrylcholinesterase nor edrophonium shortened the times from first PTC response to TOF = 0.75 compared to group 2. Neostigmine resulted in prolongation of recovery time. There was a linear relationship ($r = -0.80$; $P = 0.00001$) between PTC and time of onset of TOF response.

Conclusions: There appears to be no clinical advantage in attempting to antagonize profound mivacurium-induced neuromuscular blockade. (Key words: Antagonists, enzymes; cholinesterase: human plasma. Antagonists: edrophonium; neostigmine; neuromuscular relaxants. Monitoring: posttetanic count; train-of-four. Neuromuscular relaxants: mivacurium chloride.)

MIVACURIUM chloride is a bis-benzylisoquinolinium nondepolarizing neuromuscular blocking agent that is hydrolyzed by plasma cholinesterase (cholinesterase: E.C. 3.1.1.8, acetylcholine acylhydrolase).¹ It has a short duration of action in patients with normal plasma cholinesterase activity. Spontaneous recovery from 90% mivacurium block to 95% twitch height and train-of-four (TOF) of 0.75 normally occurs within 15 min.² These recovery times can be shortened by administration of edrophonium, neostigmine, or human plasma cholinesterase (PCHE).^{2,3} However, in profound neuromuscular blockade induced by nondepolarizing neuromuscular blocking drugs (including mivacurium), when there are no detectable responses to nerve stimulation, the administration of neostigmine or edrophonium did not affect the rate of recovery.⁴⁻⁸ Edrophonium is a weaker inhibitor of plasma cholinesterase (IC_{50} , the concentration producing 50% inhibition = $1.4 \times 10^{-3} \text{ mol} \cdot \text{l}^{-1}$) than is neostigmine ($\text{IC}_{50} = 1.0 \times 10^{-8} \text{ mol} \cdot \text{l}^{-1}$).⁹ Hart *et al.*¹⁰ noted that ad-

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ministration of edrophonium during constant infusion of mivacurium increases concentrations of mivacurium's two potent stereoisomers, *cis-trans* and *trans-trans*. Bownes *et al.*[#] have shown that antagonism of profound levels of mivacurium blockade in the cat by plasma cholinesterase was more effective than antagonism by neostigmine.

The use of PCHE for antagonism of profound mivacurium-induced blockade has not been studied in humans. Although antagonism from such intense levels of block is not normally recommended,⁵⁻⁸ in certain clinical situations it may be desired.^{11,12} Profound levels of blockade can be quantitated using the posttetanic count (PTC).¹³ A close correlation was found to exist between PTC and recovery from profound blockade induced by pancuronium, atracurium, and vecuronium.¹³⁻¹⁵ However, such a correlation has not been evaluated with mivacurium. Accordingly, we undertook a two-part study. In part 1, we examined the relationship between PTC and recovery from profound mivacurium-induced neuromuscular blockade. In part 2, we have attempted to antagonize a quantified level of profound mivacurium-induced neuromuscular blockade using either PCHE, edrophonium, or neostigmine.

Materials and Methods

After obtaining institutional approval and informed consent, 87 ASA physical status 1 or 2 patients of both sexes, aged 16-52 (mean 32.1; SD 8.2) yr and weighing 43-88 (mean 67.3; SD 10.6) kg were studied. 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 oral lorazepam 90 min before surgery. An infusion of lactated Ringer's solution was given intravenously before induction of anesthesia. The electrocardiogram, hemoglobin oxygen saturation by pulse oximetry, and arterial blood pressure were monitored. Temperature was monitored by a nasopharyngeal thermistor and maintained at $36.5 \pm 0.5^\circ\text{C}$.

Anesthesia was induced with $2 \mu\text{g} \cdot \text{kg}^{-1}$ fentanyl and $3-5 \text{ mg} \cdot \text{kg}^{-1}$ thiopental, and was maintained with 70%

nitrous oxide and 0.5-1% inspired isoflurane in oxygen. Concentrations of the 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 (end-tidal carbon dioxide pressure 35-40 mmHg).

Isoflurane was administered for 30 min before the control twitch height was recorded. The ulnar nerve was stimulated supramaximally at the wrist with square pulses of 0.2-ms duration, delivered in a train-of-four (TOF) sequence at 2 Hz every 12 s, using a Myotest peripheral nerve stimulator (Biometer International, Odense, Denmark). The resultant contraction of the adductor pollicis muscle was recorded using a force displacement transducer and neuromuscular function analyzer (Myograph 2000, Biometer). Preload tension on the thumb was maintained at 300 g throughout the investigation.

After a stable neuromuscular response was obtained, the patient received mivacurium $0.15 \text{ mg} \cdot \text{kg}^{-1}$ intravenously as a free-flowing bolus dose. No patient received additional doses of mivacurium. Tracheal intubation was performed when neuromuscular response was abolished. Four minutes after complete suppression of twitch height, the mode of stimulation was changed to 1 Hz single twitch stimulation. After 30 s, a tetanic stimulus (50 Hz) was applied for 5 s. Three seconds later, the single twitch was again applied for 30 s followed by 4 min TOF nerve stimulation. This pattern of stimulation (TOF, single twitch, tetanus, single twitch, TOF) was repeated until the time of administration of the antagonist or the first evidence of spontaneous recovery of the first twitch (T1) of the TOF was seen. Thereafter, only the TOF pattern was used to monitor recovery. This mode of stimulation was used in all patients except patients in group 1 (*vide infra*) where TOF was the only mode of stimulation used throughout the study. The PTC count is defined as the number of twitches that could be counted in the period immediately after the tetanus.

Study Paradigm

Patients were randomly allocated to eight groups.

Part 1: Temporal Relationship between Posttetanic Count and the First Reaction to Train-of-Four Stimulation and the Effect of Tetanic Stimulation on the Recovery Indexes. In group 1 (control-TOF; $n = 10$), neuromuscular function was allowed to recover spontaneously until TOF ratio (the amplitude of

Bownes PB, Hartman GS, Chiscolm D, Savarese JJ: Antagonism of mivacurium blockade by purified human butyryl cholinesterase in cats (abstract). ANESTHESIOLOGY 1992; 77:A909.

the fourth evoked response. No tetanic stimulation. Temporal relationships to TOF stimulation. Patients and the patients group. neously until (control-TOF; treated as if th in group 2.

Part 2: Antagonism of Profound Blockade

3-6, antagonism of profound blockade. muscle contraction. twitch stimulation. 4 ($n = 1$ in each group) or $1 \text{ mg} \cdot \text{kg}^{-1}$ and 6 ($n = 1$ in each group) PCHE equivalent. $\text{ml} \cdot \text{kg}^{-1}$ intravenously. Serum Cholinesterase activity, which is a direct measure of the contents of the enzyme in activity to the enzyme. However, the time of the manufacture of the enzyme from donor plasma, negative and 60°C to inactivate the enzyme with purified enzyme to those associated with albumin. In group 1, with either edrophonium or neostigmine, the first twitch of the TOF was of control. All patients who received

The TOF ratio and TOF ratio concentration were determined. Patients were given a bolus of antagonist, and at the end of the study by their ability to breathe without intubation, and

In all patients, the induction of a contralateral arm extension after administration of antagonist activity. In

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the fourth evoked response as a fraction of the first evoked response: T_4/T_1) had reached 0.75 or higher. No tetanic stimulation was used in this group. The temporal relationship between PTC and the first reaction to TOF stimulation was determined in another 21 patients, and the neuromuscular function in ten of these patients (group 2) was allowed to recover spontaneously until TOF ratio had reached 0.75 or higher (control-PTC; $n = 10$). The remaining 11 patients were treated as if they were in group 2 but were not included in group 2.

Part 2: Antagonism of Mivacurium-induced Profound and 90% Block of Twitch Height. In groups 3–6, antagonism was attempted just after detection of muscle contractions in response to posttetanic single twitch stimulation (PTC = 1 or more). Groups 3 and 4 ($n = 10$ in each) received $0.06 \text{ mg} \cdot \text{kg}^{-1}$ neostigmine or $1 \text{ mg} \cdot \text{kg}^{-1}$ edrophonium, respectively. Groups 5 and 6 ($n = 8$ in each), received exogenous human PCHE equivalent to activity present in 25 or 70 $\text{ml} \cdot \text{kg}^{-1}$ intravenous human plasma, respectively. Serum Cholinesterase P Behring was used in this study, which is a dry concentrate of highly purified enzyme. The contents of each vial (27–83 mg) are equivalent in activity to 500 ml of fresh normal human plasma. However, the cholinesterase activity is standardized by the manufacturer. The purified human PCHE is derived from donor plasma that is hepatitis B surfactant antigen-negative and anti-HIV-1-negative. It is pasteurized at 60°C to inactivate DNA viruses. The risks of treatment with purified human PCHE are considered comparable to those associated with the administration of human albumin. In groups 7 and 8 ($n = 10$ in each) antagonism with either $0.06 \text{ mg} \cdot \text{kg}^{-1}$ neostigmine or $1 \text{ mg} \cdot \text{kg}^{-1}$ edrophonium, respectively, was attempted when the first twitch of the TOF recovered spontaneously to 10% of control. Atropine ($0.02 \text{ mg} \cdot \text{kg}^{-1}$) was given to all patients who have received anticholinesterases.

The TOF ratio was recorded continuously until the TOF ratio recovered to 0.75 or more. Isoflurane concentration was maintained during antagonism. All patients were assessed in the recovery room, on admission, and at 10 min later, for signs of residual weakness by their ability to maintain 5-s head lift, tongue protrusion, and cough.

In all patients, a blood sample was taken before induction of anesthesia from an antecubital vein in the contralateral arm to that used for intravenous fluid administration for determination of plasma cholinesterase activity. In groups 3–8, two additional blood samples

were taken 3 min after the administration of the antagonist and when the TOF ratio had recovered to 0.75. Plasma cholinesterase activity was measured by the change in absorbance at 600 nm after the reduction of butyrylthiocholine to thiocholine, using du Pont Dimension, Clinical Chemistry System (Wilmington, DE).

Recovery times (times from first PTC response to TOF = 0.75) were compared using analysis of variance. Dunnett's test was used to compare the spontaneous recovery group (group 2; control-PTC) to each of the other groups. Comparisons among the groups who received different antagonists were carried out using the Student-Newman-Keuls multiple range test. Differences between group 1 (control-TOF) and group 2 (control-PTC) were determined using an unpaired Student's *t* test. Plasma cholinesterase activity (determined from the third blood sample) was correlated with both the recovery index and time of recovery of T_1 from 10% to a TOF ratio of 0.75 using Pearson's correlation coefficient. All statistical analyses were carried out using BMDP statistical software (v. 7.01, University of California Press, Berkeley, CA, 1993). Unless otherwise specified, results were expressed as means (SD), and were considered statistically significant when the *P* value was less than 0.05.

Results

Part 1: Temporal Relationship between Posttetanic Count and the First Reaction to Train-of-Four Stimulation and the Effect of Tetanic Stimulation on the Recovery Indexes. The relationship between PTC and time to first detectable response to TOF stimulation is shown in figure 1. A linear relationship fitted the data points well ($r = -0.80$; $P = 0.00001$). This relationship can be expressed as:

Time to first response to TOF (min) = $4.9 \text{ (SD } 0.42) - 0.42 \text{ (SD } 0.07) \text{ number of posttetanic twitches}$.

Because of mivacurium's short duration of action, only one, two, or three PTC determinations per patient could be made before the onset of TOF response. From this graph, the expected time of onset of TOF response can be predicted from the PTC.

Tetanic stimulation altered the subsequent neuromuscular responses. Recovery times of T_1 from 10% of control tension to a TOF ratio of 0.75 were shorter ($P < 0.01$) in group 2 (control-PTC) as compared to group 1 (control-TOF; table 1). Further, T_1 and TOF recovery (figs. 2 and 3) were significantly less in the latter group as compared to group 2 (control-PTC).

Table 1. Plasma Cholinesterase Activity, First Twitch, and Train-of-Four Recovery

Group	n	PCHE Activity (first assay)* (reference range = 7-19 units · ml ⁻¹)	Times to T1 Recovery (min)		
			25-75%	10-95%	10%, TOF = 0.75
Group 1 (control, TOF)	10	14.5 (1.8)	7.9 (4.1)	14.7 (5.4)	16.2 (4.4)
Group 2 (control, PTC)	10	13.1 (1.2)	5.7 (1.1)	11.1 (1.9)	10.4 (1.5)
P†		0.06	0.12	0.08	0.0021

Data are mean (SD).

PCHE = plasma cholinesterase; T1 = first twitch; TOF = train-of-four; PTC = number of posttetanic responses.

* Blood sample was taken before induction of anesthesia.

† Unpaired Student's *t* test.

Therefore, the control-PTC group was the control group used for comparisons with the other groups.

Part 2: Antagonism of Mivacurium-induced Profound and 90% Block of Twitch Height Baseline

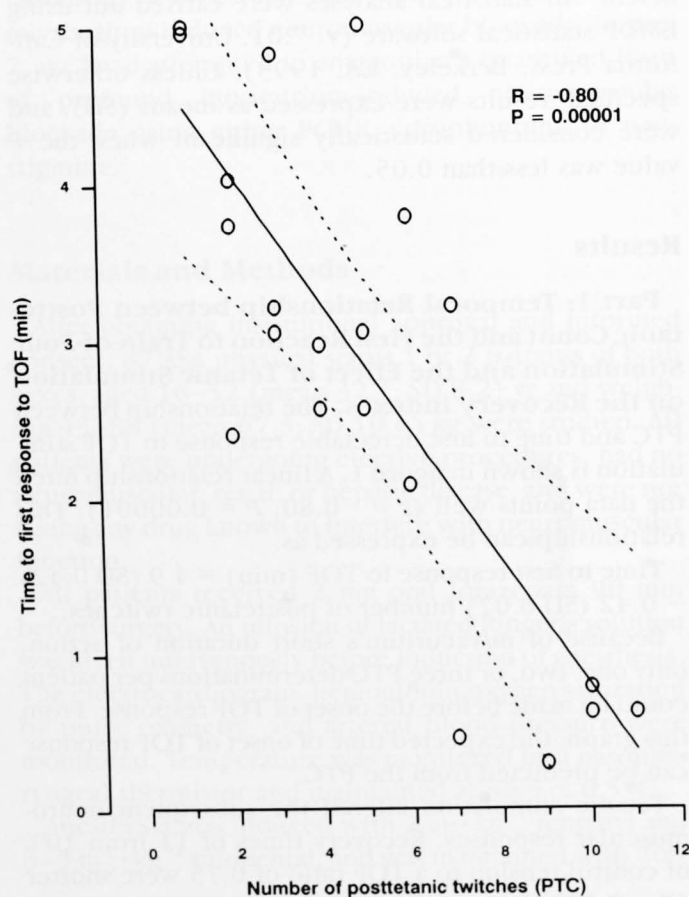


Fig. 1. Relationship between minute to first reaction to train-of-four nerve stimulation and number of posttetanic responses in 21 patients. The fitted regression line and 95% confidence intervals are given.

activity of PCHE was similar and within the normal range in all groups (reference range 7-19 units · ml⁻¹; table 2).

Human plasma cholinesterase activities measured in the second and third assays were similar. Values of the latter assay are shown in table 2. The activity in the third assay was greatest ($P < 0.01$) in patients who received exogenous PCHE (groups 5 and 6) as compared to all other groups. Administration of exogenous PCHE equivalent to activity present in 25 ml · kg⁻¹ or 70 ml · kg⁻¹ of human plasma resulted in 81.2 (24.4)% and 131.6 (33.6)% increase in the baseline PCHE activity (table 2) in groups 5 and 6, respectively. After neostigmine, PCHE activity decreased markedly ($> 90\%$; $P < 0.01$ vs. other groups).

The final T1 recovery was always within 10% of the initial control value. The times taken for first PTC response to TOF = 0.75 were significantly longer in patients who received neostigmine for antagonism of profound block induced by mivacurium (group 3) as compared to the control group (group 2, control-PTC; table 2). Likewise, recovery times were longer in group 3 as compared to patients who received edrophonium or PCHE at profound block (groups 4 and 6) or pharmacologic antagonism at 10% recovery of T1 (groups 7 and 8).

Figures 4 and 5 show first twitch height and TOF ratio recovery characteristics in each group after administration of mivacurium. At 25 and 30 min, first twitch recovery was less ($P < 0.05$) in those patients who received neostigmine at profound mivacurium block (group 3) than those in groups 2, 5, 6, 7, and 8. At these times, TOF ratio was significantly less in group 3 than that observed in groups 4-8.

There was a significant negative correlation between both the recovery index ($r = -0.33$; $P =$

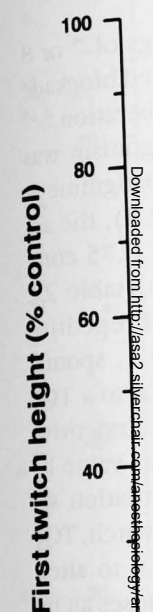


Fig. 2. Mean (± SD) first twitch height of control groups used for heteroantagonism of the first twitch compared to the control group.

0.012) and to control to a TOF ratio of 0.75. Plasma cholinesterase activity in the third assay.

Administration of 70 ml · kg⁻¹ resulted in a 131.6% increase in arterial blood pressure. Paired *t* test associated with this increase ($P = NS$) from baseline were not observed. Equivalent to plasma. There

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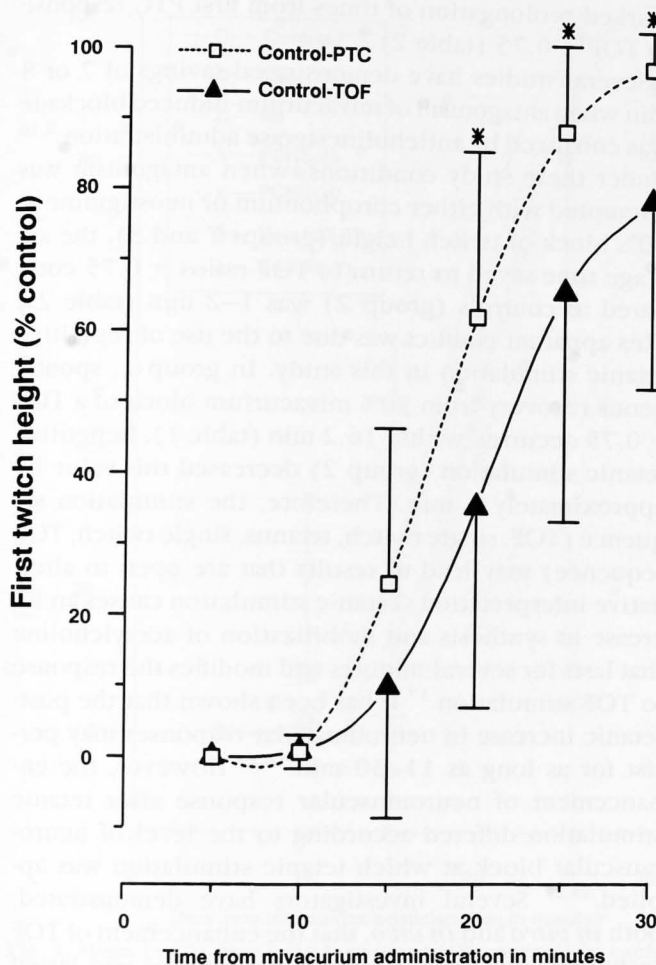


Fig. 2. Mean (\pm SD) first twitch recovery (% control) in the control groups. The use of tetanus in the stimulation sequence used for determination of posttetanic count resulted in an apparent greater recovery (i.e., underestimation of the block) of the first twitch in the control-posttetanic count group compared to the control-train-of-four group. * $P < 0.05$.

0.012) and time of recovery of T1 from 10% of control to a TOF = 0.75 ($r = -0.47$; $P = 0.0002$) and plasma cholinesterase activity as measured in the third assay.

Administration of PCHE equivalent to activity present in 70 ml \cdot kg $^{-1}$ of human plasma as an intravenous bolus resulted in a transient (<2 min) reduction in the mean arterial blood pressure (-10.3 (SD 6.4)%; $P = 0.014$; paired t test) from the preinjection value. This was associated with 8.7 (11.7)% increase in the heart rate ($P = \text{NS}$) from the preinjection value. These changes were not observed after the use of PCHE in doses equivalent to activity present in 25 ml \cdot kg $^{-1}$ of human plasma. There were no systematic differences in isoflu-

rane concentration among the groups studied and it did not vary within an individual patient. There was no indication of delayed weakness in the recovery room after anesthesia.

Discussion

The current study has demonstrated that, in patients with normal PCHE activity, there was no clinical advantage in attempting to antagonize profound mivacurium-induced neuromuscular blockade by administration of either PCHE, edrophonium, or neostigmine. Furthermore, attempted antagonism of profound blockade with neostigmine (group 3) resulted in

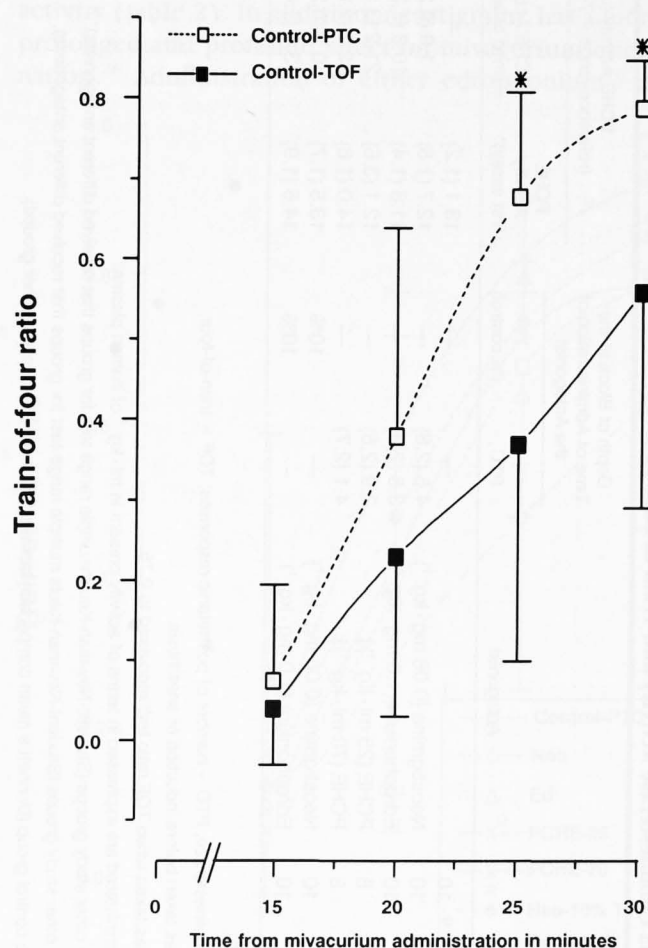


Fig. 3. Mean (\pm SD) train-of-four ratio recovery in the control groups. The use of tetanus in the stimulation sequence used for determination of posttetanic count resulted in an apparent greater recovery (i.e., underestimation of the block) of train-of-four ratio in the control-posttetanic count group compared to the control-TOF group. * $P < 0.05$.

Table 2. Plasma Cholinesterase Activity and Train-of-Four Recovery

Group	n	Antagonist	Depth of Block at the Time of Administration of the Antagonist		PCHE Activity (units · ml ⁻¹) (reference range = 7–19 units · ml ⁻¹)		Recovery Time
			PTC	T1 (% control)	PCHE Activity (first assay)*	% Change in PCHE Activity	Time from First PTC Response to TOF = 0.75 (min)
2 (control, PTC)	10	—	—	—	13.1 (1.2)	—	13.3 (2.7)
3	10	Neostigmine (0.06 mg · kg ⁻¹)	4.6 (2.8)	—	1.0 (0.2)§	-91.7 (2.2)	21.6 (12.7)**
4	10	Edrophonium (1.0 mg · kg ⁻¹)	3.8 (2.3)	—	10.8 (1.3)	-8.2 (5.5)	12.2 (3.2)§
5	8	PCHE (25 ml · kg ⁻¹)†	3.9 (2.5)	—	21.2 (3.9)†	81.2 (24.4)	16.1 (4.1)
6	8	PCHE (70 ml · kg ⁻¹)‡	4.1 (2.7)	—	32.0 (2.8)†	131.6 (33.6)	12.1 (2.3)§
7	10	Neostigmine (0.06 mg · kg ⁻¹)	—	10%	13.5 (1.7)	-93.4 (1.5)	11.6 (3.1)†
8	10	Edrophonium (1.0 mg · kg ⁻¹)	—	10%	14.6 (1.9)	-10.3 (9.1)	12.0 (3.4)§

Data are mean (SD).

PCHE = plasma cholinesterase; PTC = number of posttetanic responses; TOF = train-of-four.

* Blood sample was taken before induction of anesthesia.

† Blood sample was taken when TOF ratio had recovered to 0.75.

‡ PCHE doses administered are expressed in terms of activity present in ml · kg⁻¹ of human plasma.§ $P < 0.05$ versus other study groups (Student-Newman-Keuls multiple range test for groups that received different antagonists).† $P < 0.01$ versus other study groups (Student-Newman-Keuls multiple range test for groups that received different antagonists).** $P < 0.05$ versus control group (Dunnett's mean comparison between the control group and other groups).

marked prolongation of times from first PTC response to TOF = 0.75 (table 2).

Several studies have demonstrated savings of 7 or 8 min when antagonism of mivacurium-induced blockade was enhanced by anticholinesterase administration.^{2,16} Under these study conditions, when antagonism was attempted with either edrophonium or neostigmine at 90% block of twitch height (groups 7 and 8), the average time saved to return to TOF ratios = 0.75 compared to controls (group 2) was 1–2 min (table 2). This apparent conflict was due to the use of repetitive tetanic stimulation in this study. In group 1, spontaneous recovery from 90% mivacurium block to a TOF = 0.75 occurred within 16.2 min (table 1). Repetitive tetanic stimulation (group 2) decreased this value by approximately 6 min. Therefore, the stimulation sequence (TOF, single twitch, tetanus, single twitch, TOF sequence) may lead to results that are open to alternative interpretation. Tetanic stimulation causes an increase in synthesis and mobilization of acetylcholine that lasts for several minutes and modifies the response to TOF stimulation.¹⁷ It has been shown that the post-tetanic increase in neuromuscular responses may persist for as long as 11–30 min.^{18,19} However, the enhancement of neuromuscular response after tetanic stimulation differed according to the level of neuromuscular block at which tetanic stimulation was applied.^{20,21} Several investigators have demonstrated, both *in vitro* and *in vivo*, that the enhancement of TOF responses after tetanic stimuli was greater and lasted longer at intense levels of neuromuscular block than at light levels.^{20–22}

Bownes *et al.*⁸ noted that neostigmine was effective in antagonizing mivacurium when reversal was attempted at 90% block of twitch height, and in the presence of 100% twitch inhibition, the enzymatic reversal through increased metabolism was more effective than antagonism by neostigmine. The short duration of action of mivacurium is primarily related to its hydrolysis by PCHE.²³ Administration of exogenous PCHE during profound block induced by mivacurium will, therefore, enhance hydrolysis of mivacurium in the plasma. As the plasma concentration of mivacurium declines, there will be a net movement of mivacurium from the neuromuscular junction back into the blood. This will accelerate the recovery of the neuromuscular function. In accordance with our previously published results,³ this study also has shown a significant negative correlation between different recovery times and the increases in patient's PCHE activity.

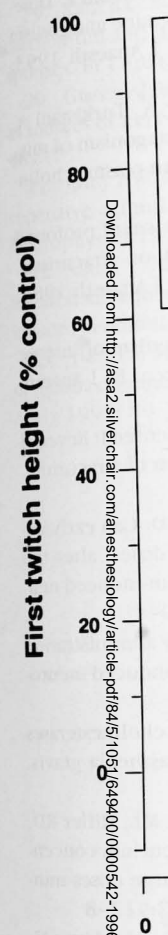


Fig. 4. Mean (SD) first twitch height of control group.

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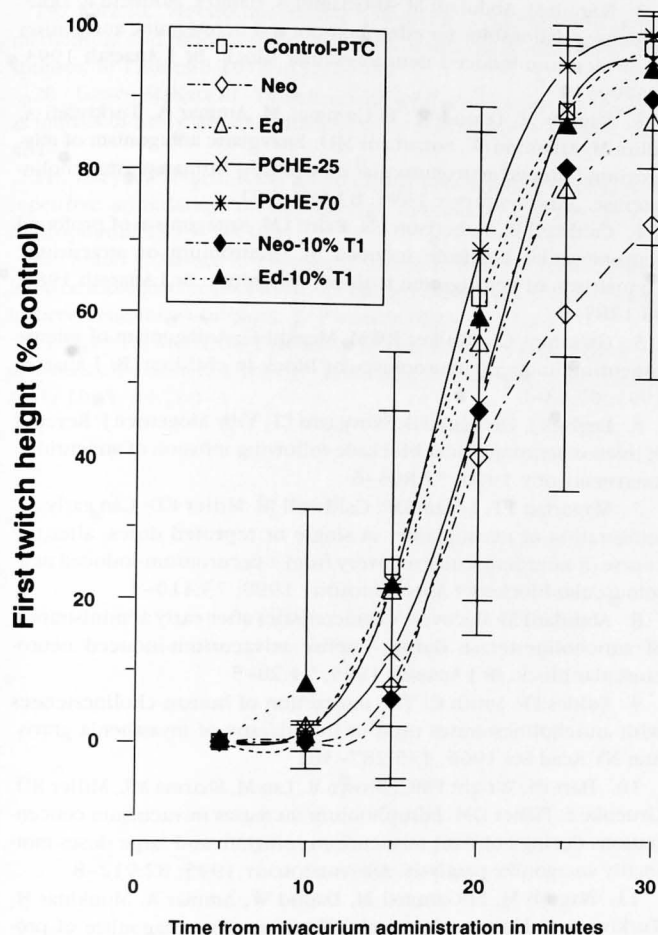


Fig. 4. Mean (\pm SD) first twitch recovery (% control) in each group.

The preparation of PCHE used by Bownes *et al.*[#] was different from that used in this study (Savarese JJ; personal communication). They noted, in cats, that 12.5 mg of their preparation significantly shortened the recovery times.[#] Although they did not measure the increases in PCHE activity, the same group reported in another study that 9.2 mg of this preparation resulted in a 269-fold increase in baseline activity of PCHE.²⁴ The doses of PCHE used in this study (equivalent to activity present in 25 ml \cdot kg⁻¹ or 70 ml \cdot kg⁻¹ of human plasma) resulted in 81.2 (24.4)% and 131.6 (33.6)% increase in the baseline PCHE activity, respectively (table 2). These doses in a 65-kg patient represent, on average, the equivalence of PCHE activity of 1625 and 4550 ml of adult human plasma, respectively. However, the increase in PCHE activity noted in this study was not sufficient to produce significant acceleration of recovery variables as compared to the control group

(table 2). It is possible that increasing the doses of PCHE further might have enhanced the recovery of profound mivacurium-induced blockade. However, the limitations of this approach are the cost³ and the undesirable effects on the hemodynamic variables, as noted in this study.

The doses of neostigmine and edrophonium used in this study were equipotent (during nonsteady-state conditions).² Edrophonium has been shown to be less effective than neostigmine in the antagonism of profound blocks induced by vecuronium,⁴ atracurium,⁴ or pancuronium.²⁵ However, our findings indicate that edrophonium was more effective than neostigmine in antagonizing profound mivacurium-induced block. This can be explained by the finding that neostigmine (but not edrophonium) significantly inhibited PCHE activity (table 2). In addition, neostigmine has a more prolonged and profound effect on mivacurium elimination.²⁶ Administration of either edrophonium¹⁰ or

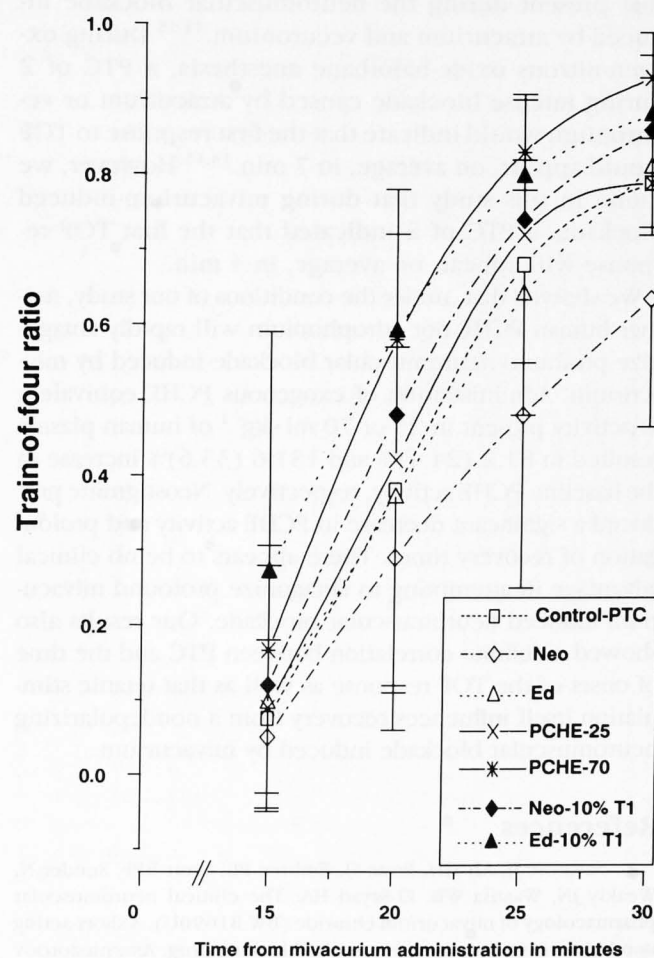


Fig. 5. Mean (\pm SD) train-of-four ratio recovery in each group.

neostigmine²⁶ during constant infusion of mivacurium resulted in increase in plasma mivacurium concentrations. However, 8 min after antagonism, edrophonium's effect on mivacurium elimination had resolved whereas the effect of neostigmine persisted (and increased). Further, neostigmine, by its direct agonistic effects, might block acetylcholine receptor-operated ion channel.²⁷ Although it has been reported that, during profound mivacurium-induced blockade, edrophonium was a more effective antagonist than neostigmine when antagonism was attempted at a PTC of 0, yet, contrary to our results no difference was detected when antagonism was attempted after detection of PTC.⁸

Our results show a definite correlation between PTC and the time of onset of the TOF response (fig. 1). The response to posttetanic twitch stimulation appeared, on average, 4.5 min before the first detectable response to TOF stimulation. The relationship between PTC and TOF found with mivacurium (in this study) differs from that present during the neuromuscular blockade induced by atracurium and vecuronium.^{14,15} During oxygen-nitrous oxide-halothane anesthesia, a PTC of 2 during intense blockade caused by atracurium or vecuronium would indicate that the first response to TOF would appear, on average, in 7 min.^{14,15} However, we found in this study that during mivacurium-induced blockade, a PTC of 2 indicated that the first TOF response will appear, on average, in 4 min.

We showed that, under the conditions of our study, neither human PCHE nor edrophonium will rapidly antagonize profound neuromuscular blockade induced by mivacurium. Administration of exogenous PCHE equivalent to activity present in 25 or 70 ml · kg⁻¹ of human plasma resulted in 81.2 (24.4)% and 131.6 (33.6)% increase in the baseline PCHE activity, respectively. Neostigmine produced a significant decrease in PCHE activity and prolongation of recovery times. There appears to be no clinical advantage in attempting to antagonize profound mivacurium-induced neuromuscular blockade. Our results also showed a definite correlation between PTC and the time of onset of the TOF response as well as that tetanic stimulation itself influences recovery from a nondepolarizing neuromuscular blockade induced by mivacurium.

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