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Enzymatic Antagonism of Mivacurium-induced Neuromuscular Blockade by Human Plasma Cholinesterase

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Background: **Mivacurium chloride is a bis-benzylisoquinolinium nondepolarizing neuromuscular blocking agent, hydrolyzed by butyrylcholinesterase (PCHE). The dose-response relationships for PCHE after mivacurium have not been studied. Therefore, this study was designed to establish dose-response relationships for PCHE as an antagonist of mivacurium-induced neuromuscular blockade.**

Methods: **Forty-eight physical status 1 adults were given 0.15 mg/kg mivacurium during fentanyl-thiopental-nitrous oxide-isoflurane anesthesia. Train-of-four (TOF) stimulation was applied to the ulnar nerve every 12 s, and the force of contraction of the adductor pollicis muscle was recorded. When spontaneous recovery of first twitch height (T1) reached 10% of its initial control value, exogenous PCHE equivalent to activity present in 2.5, 5, 7.5, 15, or 25 ml/kg of human plasma was administered by random allocation to 40 patients. Neuromuscular function in another eight subjects was allowed to recover spontaneously. Two blood samples were taken for determination of plasma cholinesterase activity. The first sample was taken before induction of anesthesia, and the second sample was taken when the TOF ratio had recovered to 0.75. Dibucaine and fluoride numbers were determined from the first assay.**

Results: **Administration of PCHE produced significant increases in PCHE activity in all patients. The larger the dose, the greater was the resultant plasma activity. Human PCHE produced a dose-dependent antagonism of mivacurium-induced neuromuscular blockade and the recovery times correlated inversely with PCHE activity ($P < 0.01$). The recovery of T1 was greater ($P < 0.01$) and time to attain a TOF ratio of 0.75 was shorter ($P < 0.01$) with any dose of PCHE than that observed in the spontaneous recovery group. After the administration of exogenous PCHE equivalent to activity present in 25 ml/kg of human plasma, recovery of TOF ratio to 0.75 or more was observed in all patients in less than 10 min and time to attain a TOF ratio of 0.75 was 55% shorter than the spontaneous recovery group (8.4 [7.1–9.7] *vs.* 18.7 [15.4–22] min; mean and 95% confidence intervals).**

Conclusions: **Administration of exogenous PCHE equivalent to activity present in 25 ml/kg of human plasma (in a 65-kg patient, this dose is equivalent to PCHE activity of 1,625 ml of adult human plasma) resulted in reliable antagonism of mivacurium-induced neuromuscular blockade. Nevertheless, because of the prohibitive cost of this compound, this reversal modality is unlikely to have a routine practical application at this time. (Key words: Antagonists: enzymes; human plasma cholinesterase; neuromuscular relaxants. Monitoring: train-of-four. Neuromuscular relaxants: mivacurium chloride.)**

MIVACURIUM chloride is a bis-benzylisoquinolinium nondepolarizing neuromuscular blocking agent, hydrolyzed by plasma cholinesterase (cholinesterase: E.C. 3.1.1.8, acetylcholine acylhydrolase).[1] Because both this enzyme and acetylcholinesterase are inhibited by neostigmine and pyridostigmine,[2] enzymatic antagonism of mivacurium-induced neuromuscular block with human plasma cholinesterase would eliminate the concern regarding the antagonistic effect of neostigmine on metabolism of mivacurium.

This study was designed to establish the reversal characteristics of mivacurium after different doses of human plasma cholinesterase (PCHE).

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No reprints will be available.

Materials and Methods

After obtaining institutional
consent, we studied 48 ASA ph
of both sexes, aged 16–53 (m
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Materials and Methods

After obtaining institutional approval and informed consent, we studied 48 ASA physical status 1 patients of both sexes, aged 16–53 (mean 29.1 ± 9.8) yr and weighing 45–90 (mean 64.8 ± 10.9) kg. 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 operation. An infusion of lactated Ringer's solution was given intravenously before induction of anesthesia. The electrocardiogram, hemoglobin O_2 saturation by pulse oximetry (Sp_{O_2}), and arterial blood pressure were monitored. Temperature was monitored by a nasopharyngeal thermistor and maintained at 36.5 ± 0.5°C.

Anesthesia was induced with 2 μg/kg fentanyl and 3–5 mg/kg 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 CO_2 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 International, Odense, Denmark). Preload tension on the thumb was maintained at 300*g* throughout the investigation.

After a stable neuromuscular response was obtained for 10 min, the patient received 0.15 mg/kg mivacurium intravenously as a free-flowing bolus dose. Tracheal intubation was performed when neuromuscular response was abolished. Additional increments of 0.1 mg/kg mivacurium 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 were randomly allocated to six groups (n = 8 in each). Neuromuscular function in patients in group 1 (control group) was allowed to recover spontaneously, whereas patients in groups 2–6 received exogenous human PCHE equivalent to activity present in 2.5, 5, 7.5, 15, or 25 ml/kg of human plasma intravenously, respectively. Serum Cholinesterase P Behring, which is a dry concentrate of highly purified enzyme, was used in this study. 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. Heart rate was recorded every minute after PCHE administration for 10 min. The TOF ratio (the amplitude of the fourth evoked response as a fraction of the first evoked response: T4/T1) was recorded continuously in all patients until the TOF ratio recovered to 0.75. If the final T1 was not close to the initial control, the final T1 value achieved was accepted as control and all other T1 values measured during recovery were normalized according to this standard. All patients were assessed in the recovery room, on admission, and at 10 min later, for signs of residual paralysis by their ability to maintain 5-s head lift, tongue protrusion, and cough.

In all patients, two blood samples were taken from an antecubital vein in the contralateral arm to that used for intravenous fluid administration for determination of plasma cholinesterase activity, dibucaine, and fluoride numbers. The first sample was taken before induction of anesthesia, and the second sample was taken when the TOF ratio had recovered to 0.75. The dibucaine and fluoride numbers were determined from the first sample. 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).

We used linear regression analysis to determine the dose-response relation for both T1 and TOF ratio. 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 whether the elevations were different. If so, a *t* test was applied to determine which line differed in elevation[3] (BMDP statistical package, release 7.01, University of California Press, Berkeley, CA).

Recovery times of the first twitch from 25–75% (recovery index) and 10–95% of control, and time to a TOF ratio of 0.75, were compared using ANOVA. Dun-

nett's test was used to compare the spontaneous recovery group with each of the other groups. Comparisons between the groups who received different doses of PCHE were carried out using the Tukey Studentized Range method. Plasma cholinesterase activity (determined from the second blood sample) was correlated with both the recovery index and time to a TOF of 0.75 using Pearson's correlation coefficient. Unless otherwise specified, results were expressed as means and 95% confidence intervals, and were considered statistically significant when the P value was less than 0.05.

Results

Baseline activity of PCHE was similar in all groups (reference range 7–19 units/ml; table 1). The activity in the second assay was greatest ($P < 0.01$) in groups 5 and 6 compared with all other groups. Administration of exogenous PCHE equivalent to activity present in 25 ml/kg of human plasma (group 6) resulted in 89% (81–96%) increase in the baseline PCHE activity (table 1). For the patients in group 5, the increase was 56% (48–64%).

The final T1 recovery was always within 10% of the initial control value. Figures 1 and 2 show first twitch height and train-of-four ratio as a function of time after administration of PCHE. At all doses, the effect of PCHE was sustained. First twitch recovery was greater in those patients who received PCHE than in those allowed to recover spontaneously. In the first 3 min after the administration of PCHE, the first twitch was significantly ($P < 0.05$) greater in those patients who received exogenous PCHE equivalent to activity present in 15 and 25 ml/kg of human plasma than in the spontaneous recovery group (fig. 1). However, from 4 to 10 min, the first twitch recovery was significantly ($P < 0.01$) greater in all groups who received PCHE than in those allowed to recover spontaneously (fig. 1). The differences in the first twitch recovery characteristics observed in patients who received different doses of PCHE were not statistically significant.

In the first 10 min after the administration of PCHE, TOF recovery was significantly ($P < 0.01$) greater in patients in group 6 who received exogenous PCHE equivalent to activity present in 25 ml/kg of human plasma than in those in the spontaneous recovery group (fig. 2). Patients in group 5, who received exogenous PCHE equivalent to activity present in 15 ml/kg of human plasma, demonstrated a greater ($P < 0.05$) TOF recovery than did patients in the spontaneous recovery

Table 1. Plasma Cholinesterase (PCHE) Activity, First Twitch (T1), and Train-of-Four (TOF) Recovery from 10% Block

Group No.	n	PCHE Activity (first assay)* (reference range = 7–19 units/ml)	PCHE Dose Administered (expressed in terms of activity present in ml/kg of human plasma)	PCHE Activity (second assay)† (units/ml)	Percent Increase in PCHE Activity	T1 at 10 min (% control)	TOF Ratio at 10 min	Times to T1 Recovery (min) 25–75%	Times to T1 Recovery (min) 10–95%	Time to TOF = 0.75 (min)
1 (spontaneous recovery group)	8	12.3 (10.5–14.1)	0	12.1 (10.3–14)		62.6 (49.6–75.7)	0.47 (0.39–0.55)	8.6 (6–11.2)	18.4 (14.2–22.7)	18.7 (15.4–22)
2	8	11.6 (9.7–13.4)	2.5	12.1 (10.1–13.9)	4 (3–5)	93.3 (86.3–100)‡	0.59 (0.51–0.68)	5.1 (3.7–6.5)‡	8.8 (7.0–10.7)‡	13.5 (10.8–16.2)‡
3	8	11.9 (10.7–13.3)	5	13.9 (12.4–15.4)	16 (11–22)	98.9 (96.6–101)‡	0.61 (0.49–0.72)	4.1 (3.8–4.4)‡	7.4 (6.4–8.5)‡	12.4 (10.1–14.6)‡
4	8	10.1 (8.2–12.1)	7.5	12.7 (10.9–14.6)	28 (18–37)	96.8 (90.4–103)‡	0.57 (0.41–0.73)	4.0 (3.2–4.9)‡	7.8 (6.0–9.7)‡	12.9 (9.8–15.4)‡
5	8	12.5 (11.3–13.6)	15	19.4 (18.4–20.3)‡	56 (48–64)	99.0 (96.6–101)‡	0.66 (0.55–0.78)§	4.3 (3.8–4.8)‡	7.9 (7.2–8.7)‡	11.5 (8.5–14.4)‡
6	8	12.4 (10.7–14.1)	25	23.4 (20.3–26.4)‡	89 (81–96)	99.3 (96.2–102)‡	0.81 (0.76–0.86)‡	3.6 (2.8–4.4)‡	6.6 (5.2–8.1)‡	8.4 (7.1–9.7)‡

Data are presented as means (95% confidence intervals).

* Blood sample was taken before induction of anesthesia.

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

‡ $P < 0.01$ *versus* the spontaneous recovery group.

§ $P < 0.05$ *versus* the spontaneous recovery group.

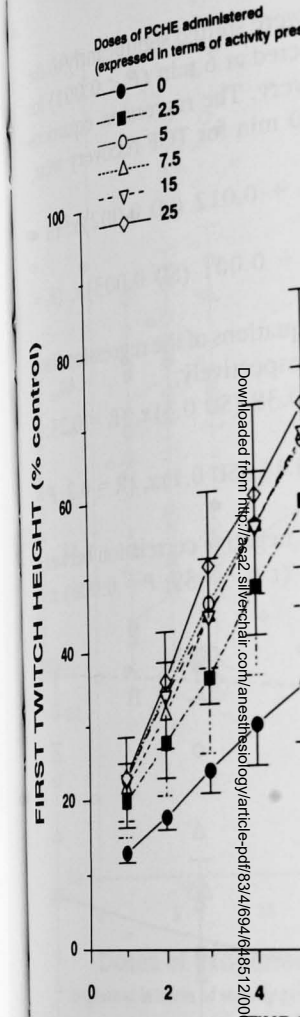

Fig. 1. Mean (± SD) first twitch h
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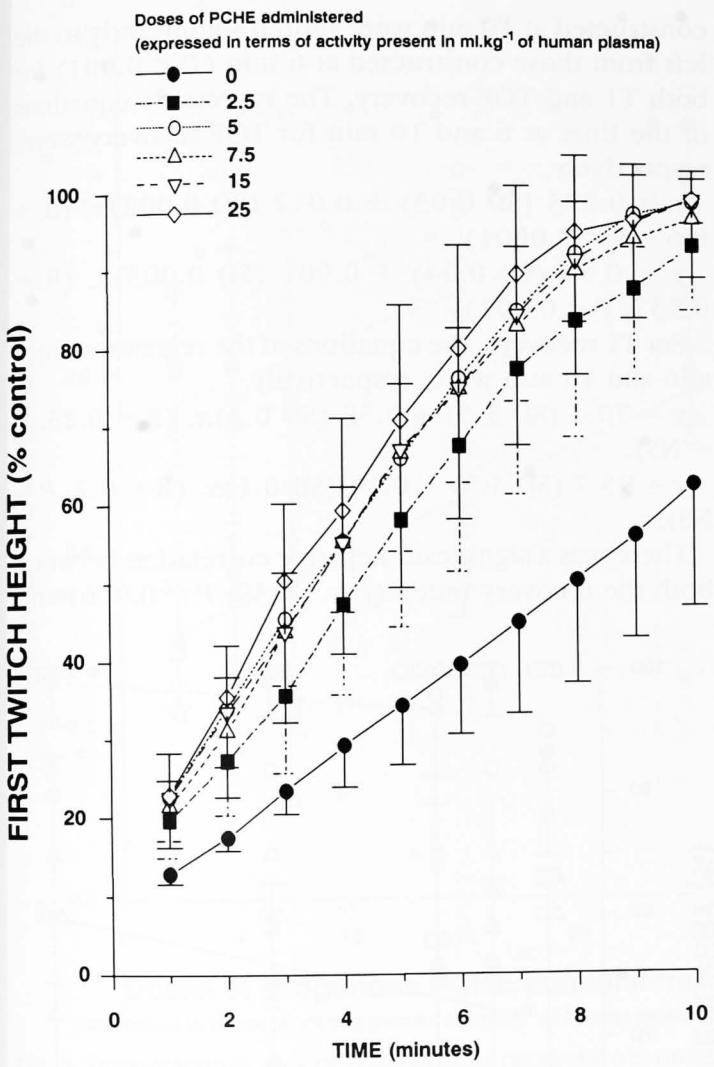

Fig. 1. Mean (± SD) first twitch height *versus* time after administration of various doses of human plasma cholinesterase or in the spontaneous recovery group (0). Antagonism of neuromuscular blockade was attempted when first twitch height reached 10% of its control value.

group after 7 min. Five minutes after the administration of PCHE, TOF recovery observed in groups 2, 3, and 4 was significantly ($P < 0.05$) less than that observed in groups 5 and 6 (fig. 2).

First twitch recovery at 10 min was greater ($P < 0.01$) in patients who received PCHE than in those who were allowed to recover spontaneously (fig. 1 and table 1). Similar observations were noted for the train-of-four recovery (fig. 2 and table 1). Likewise, times taken for the twitch height to recover from 25 to 75% and 10 to 95% of the control value and for TOF ratio to recover to 0.75 were significantly longer in the spontaneous recovery group as compared with other groups (fig. 3 and table 1). In the absence of antagonism, the mean time required to attain a TOF ratio of 0.75 in the spontaneous recovery group was 18.7 (15.4–22) min. This was longer ($P < 0.01$) than that observed in other groups who received PCHE (table 1). All patients in group 6 had recovered to a TOF ratio of 0.75 or more in less than 10 min (table 1). At this time, the recovery of the TOF ratio in the latter group was significantly ($P < 0.01$) greater than that observed in groups 2–4.

One patient in group 4 was found to be heterozygous for the dibucaine resistant gene (dibucaine number 70.6; normal range 80–88). This patient had a fluoride number of 50 (normal range 45–55) and a PCHE activity of 5.61 units/ml, which increased to 8.01 units/ml after administration of exogenous PCHE equivalent to activity present in 7.5 ml/kg of human plasma (total

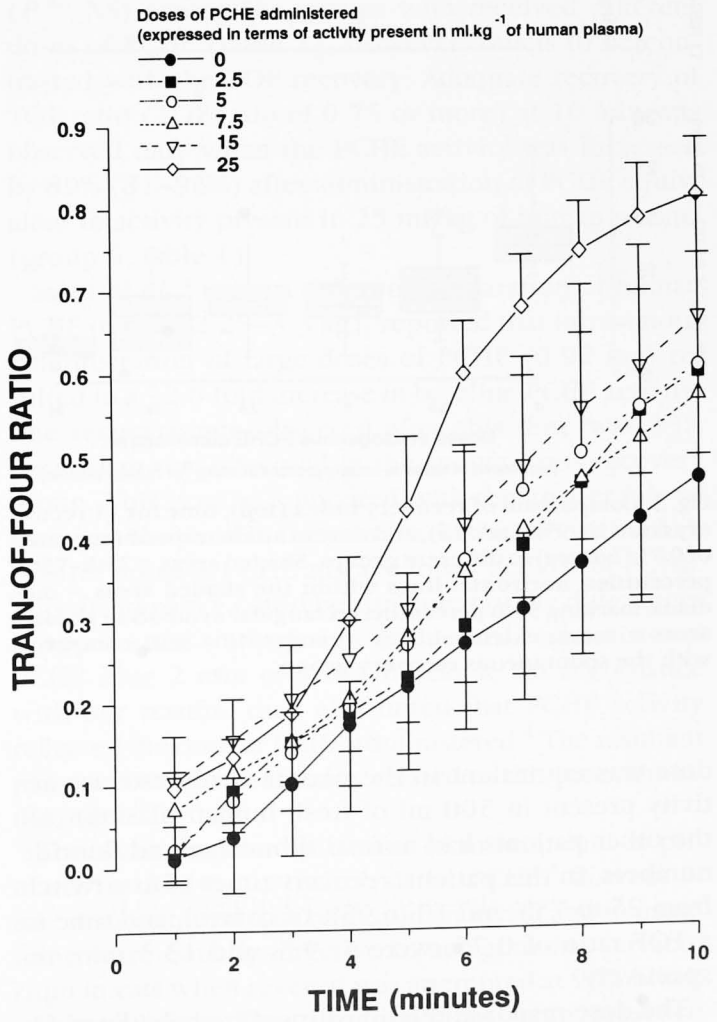

Fig. 2. Mean (± SD) train-of-four ratio *versus* time after administration of various doses of human plasma cholinesterase or in the spontaneous recovery group (0). Antagonism of neuromuscular blockade was attempted when first twitch height reached 10% of its control value.

3	8	11.9 (10.7–13.3)	0.61 (0.49–0.72)	4.1 (3.8–4.4)‡	7.4 (6.4–8.5)‡	16 (11–22)	98.9 (96.6–101)‡
4	8	10.1 (8.2–12.1)	0.57 (0.41–0.73)	4.0 (3.2–4.9)‡	7.8 (6.0–9.7)‡	28 (18–37)	96.8 (90.4–103)‡
5	8	12.5 (11.3–13.6)	0.66 (0.55–0.78)§	4.3 (3.8–4.8)‡	7.9 (7.2–8.7)‡	56 (48–64)	99.0 (96.6–101)‡
6	8	12.4 (10.7–14.1)	0.81 (0.76–0.86)‡	3.6 (2.8–4.4)‡	6.6 (5.2–8.1)‡	89 (81–96)	99.3 (96.2–102)‡

Data are presented as means (95% confidence intervals).
* Blood sample was taken before induction of anesthesia.
† Blood sample was taken when TOF ratio had recovered to 0.75.
‡ $P < 0.01$ versus the spontaneous recovery group.
§ $P < 0.05$ versus the spontaneous recovery group.

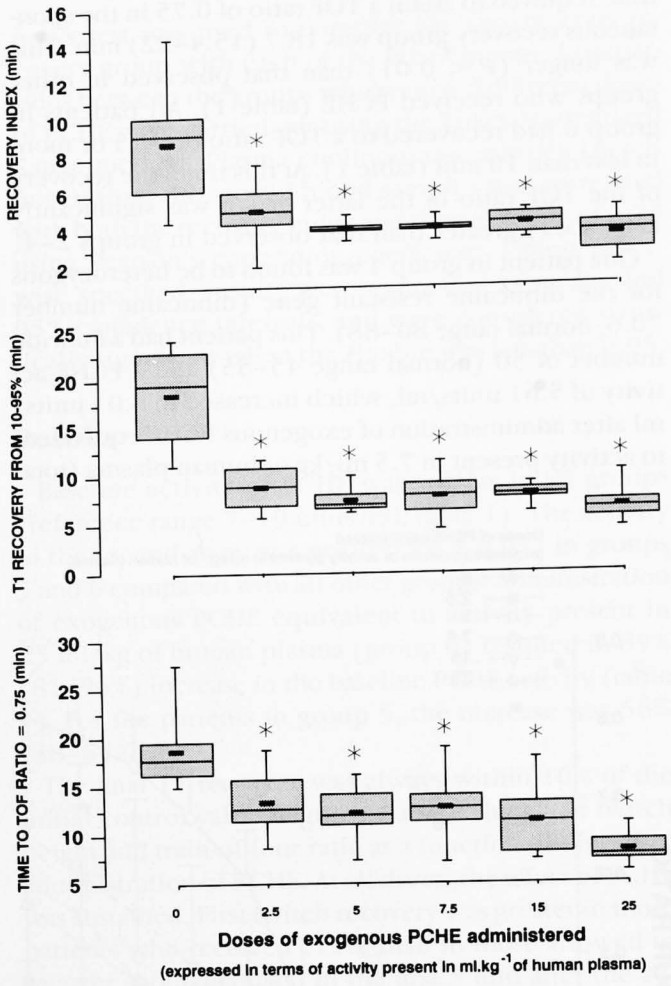

Fig. 3. Comparison of recovery index (*top*), time for T1 recovery from 10–95% (*middle*), and time to attain train-of-four ratio of 0.75 (*bottom*) in different groups. Shaded areas = 25th–75th percentiles; horizontal lines within the shaded areas = medians, marking 50th percentile; rectangular symbols in shaded areas = mean; extended bars = ranges. *$P < 0.01$ compared with the spontaneous recovery group.

dose was equivalent to the plasma cholinesterase activity present in 500 ml of fresh human plasma). All the other patients had normal dibucaine and fluoride numbers. In this patient, recovery times of first twitch from 25 to 75% and 10 to 95% of control, and time to a TOF ratio of 0.75, were 5, 9.3, and 13.3 min, respectively.

The dose-response relationships were calculated for each minute after the administration of the antagonist. Mean data for the T1 and TOF responses at 6 and 10 min are shown in figures 4 and 5, respectively. The lines did not deviate from parallelism, but the lines constructed at 10 min were shifted significantly to the left from those constructed at 6 min ($P < 0.001$) for both T1 and TOF recovery. The regression equations of the lines at 6 and 10 min for TOF recovery were, respectively,

$y = 0.273$ (SD 0.03) + 0.012 (SD 0.002)x, (R = 0.67, $P < 0.0001$),

$y = 0.54$ (SD 0.04) + 0.001 (SD 0.003)x, (R = 0.537, $P < 0.001$).

For T1 recovery, the equations of the regression lines at 6 and 10 min were, respectively,

$y = 70.4$ (SD 3.6) + 0.38 (SD 0.3)x, (R = 0.23, P = NS),

$y = 95.7$ (SD 1.5) + 0.14 (SD 0.1)x, (R = 0.2, P = NS).

There was a significant negative correlation between both the recovery index (r = −0.39; $P = 0.006$) and

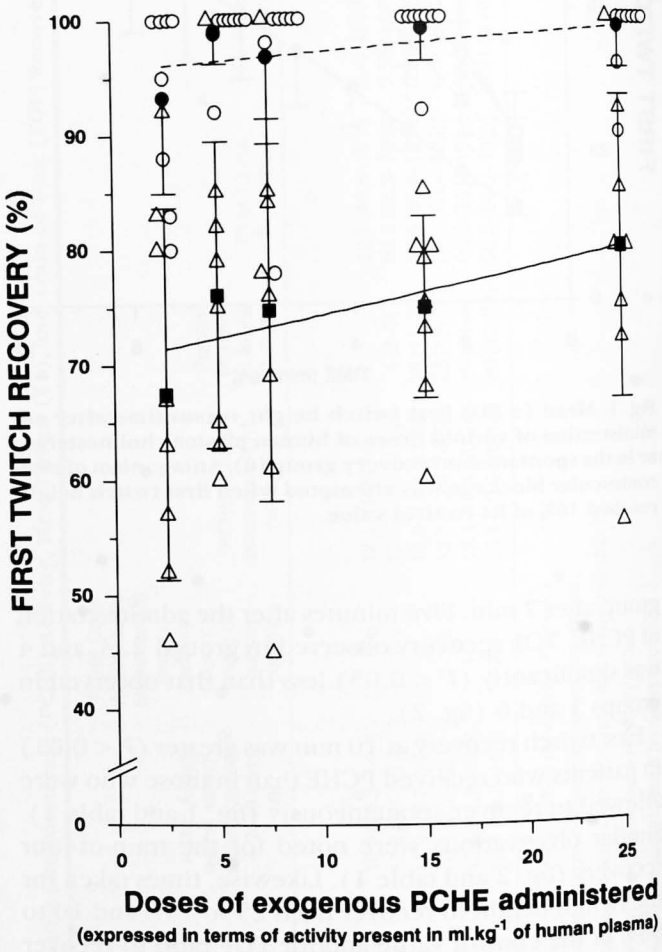

Fig. 4. Dose-response plot of first twitch recovery (percent control) obtained at 6 min (△ — △) and at 10 min (○ - - ○) after administration of human plasma cholinesterase. Black symbols = mean T1 attained with each dose; bars = SD.

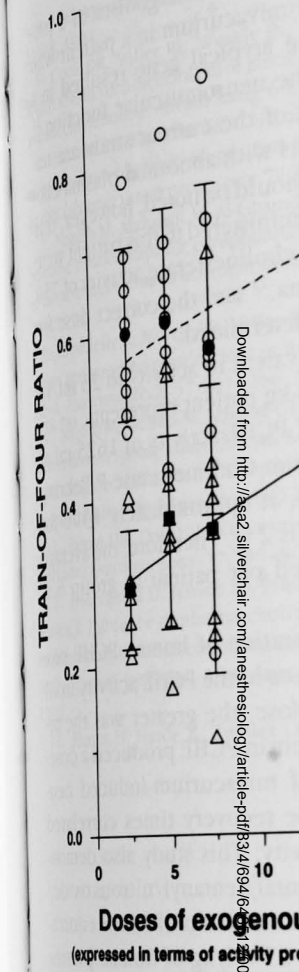

Fig. 5. Dose-response plot of trai
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Administration of PCHE wa
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There was no indication of de
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Discussion

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twitch height was greater (P <
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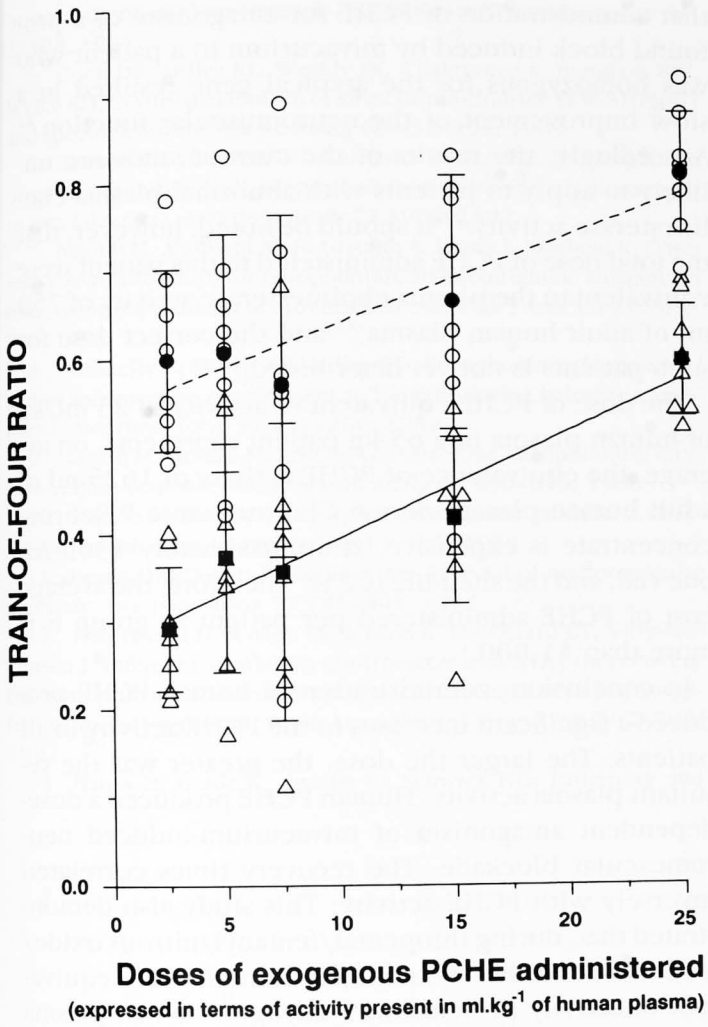

Fig. 5. Dose-response plot of train-of-four recovery obtained at 6 min (△ — △) and 10 min (○ - - ○) after administration of human plasma cholinesterase. Black symbols = mean train-of-four attained with each dose; bars = SD.

time to TOF ratio = 0.75 ($r = -0.54$; $P = 0.00008$) and plasma cholinesterase activity measured in the second assay.

Administration of PCHE was not associated with any significant changes in the hemodynamic parameters. There was no indication of delayed paralysis in the recovery room after anesthesia.

Discussion

This study demonstrated that the recovery of the first twitch height was greater ($P < 0.01$) and time to attain a TOF ratio to 0.75 was shorter ($P < 0.01$) with any dose of PCHE than that observed in the spontaneous recovery group (fig. 3 and table 1). After administration of PCHE equivalent to activity present in 25 ml/kg of human plasma (group 6), recovery to a TOF ratio of 0.75 was 55% shorter than in the spontaneous recovery group (8.4 *vs.* 18.7 min), and in group 5 (after administration of PCHE equivalent to activity present in 15 ml/kg of human plasma), recovery was approximately 40% shorter (11.5 *vs.* 18.7 min; table 1).

Small doses of PCHE were capable of reversing twitch depression but not the TOF fade. For example, administration of PCHE equivalent to activity present in 2.5 ml/kg of human plasma (group 2) increased PCHE activity by only 4% (3–5%) (P = NS), but it shortened the 10–95% recovery time from 18.4 to 8.8 min ($P < 0.01$; table 1). Increasing the dose of PCHE (groups 5 and 6) did not improve this index of recovery. In fact, the 25–75% and 10–95% recovery times were similar (P = NS) among the groups who received different doses of PCHE (table 1). However, this is to be contrasted with the TOF recovery. Adequate recovery of TOF ratio (TOF ratio of 0.75 or more) at 10 min was observed only when the PCHE activity was increased by 89% (81–96%) after administration of PCHE equivalent to activity present in 25 ml/kg of human plasma (group 6; table 1).

Stout *et al.*,[4] using a different preparation of human PCHE in cats (2.25–3.3 kg), reported that intravenous administration of large doses of PCHE (0.92 mg) resulted in a 22.6-fold increase in baseline PCHE activity. The recovery rate observed after this dose was 33% faster than that observed in the spontaneous recovery group. This is to be compared with the greater rate of recovery observed in humans (in this study) with much smaller doses of PCHE and at a lower activity of PCHE. This discrepancy could be attributed to the differences in species and study design. Stout *et al.*[4] administered PCHE after 2 min of 100% blockade. In accordance with our results, they also noted that PCHE activity reflected the dose of PCHE administered.[4] The resultant plasma activity was linearly related to the dose administered.

The short duration of action of mivacurium is primarily related to its hydrolysis by PCHE.[5] Bownes *et al.*[6] demonstrated that both human PCHE and neostigmine were equally effective in antagonizing mivacurium in cats when reversal was attempted at 90% block of twitch height. They also found that, in the presence of 100% twitch inhibition, the enzymatic reversal through increased metabolism was more effective than antagonism by neostigmine.[6] Our previously reported results with neostigmine and edrophonium antagonism

of mivacurium-induced block[7] (using the same protocol described in this report) demonstrate that the maximum TOF ratio attained at 10 min was 0.84 (0.75–0.93) and 0.78 (0.66–0.89) after 0.4 and 1 mg/kg edrophonium, respectively. Corresponding values after 0.02 and 0.05 mg/kg neostigmine were 0.78 (0.68–0.88) and 0.77 (0.69–0.85), respectively. Nevertheless, adequate recovery of TOF ratio (TOF ratio = 0.75) at 10 min was not observed in all patients in that study.[7] Furthermore, the antagonistic effect of the increasing doses of neostigmine was evident.[7] The TOF recovery was faster in patients who received 0.02 mg/kg neostigmine than in those who received 0.05 mg/kg neostigmine (times to TOF = 0.75 were, respectively, 7.5 [5.9–7.1] and 8.1 [6.4–9.8] min).[7] In the current study, however, all patients who received exogenous PCHE equivalent to activity present in 25 ml/kg of human plasma (group 6) had recovered to a TOF ratio of 0.75 or more by 10 min (table 1). Therefore, enzymatic antagonism is more efficacious than is pharmacologic antagonism, and it would eliminate the concern regarding the antagonistic effect of neostigmine on metabolism of mivacurium. In addition, unlike PCHE, administration of pharmacologic antagonists (anticholinesterases) with anticholinergic drugs is associated with undesirable cardiovascular,[8–10] intestinal, neuromuscular, and respiratory effects (for review see Bevan *et al.*[11]).

This study has shown a significant negative correlation between different recovery times and the increases in patient's PCHE activity. Increasing PCHE activity in the patient's blood enhanced the antagonism of mivacurium. Østergaard *et al.*[12] showed a negative correlation between PCHE activity and time to return of the first twitch after a bolus dose of 0.2 mg/kg, although they could not demonstrate a correlation when a dose of 0.1 mg/kg was used.

The plasma cholinesterase molecule is a tetramer of four identical subunits, each containing 574 amino acids with a total weight of approximately 342,000 Daltons.[13,14] The half-life of plasma cholinesterase administered to patients with enzyme deficiency is approximately 10–11 days.[15,16] The enzyme preparation produced by Behringwerke excludes the presence of hepatitis virus or HIV-induced AIDS and no anaphylactoid reactions have been observed until now.

Serum Cholinesterase P Behring has been used to reverse the prolonged block induced by succinylcholine[17–20] and mivacurium[21] in patients with atypical plasma cholinesterase. We recently reported that administration of PCHE for antagonism of a profound block induced by mivacurium in a patient who was homozygous for the atypical gene resulted in a slow improvement of the neuromuscular function.[21] Accordingly, the results of the current study are unlikely to apply to patients with abnormal plasma cholinesterase activity.[21] It should be noted, however, that the total dose of PCHE administered to this patient were equivalent to the plasma cholinesterase activity of 750 ml of adult human plasma,[21] and the correct dose for such patients is not yet determined.

The dose of PCHE equivalent in activity to 25 ml/kg of human plasma in a 65-kg patient represents, on average, the equivalence of PCHE activity of 1625 ml of adult human plasma. Serum Cholinesterase P Behring concentrate is expensive, at approximately $300 for one vial, and the shelf life is 2 yr. Therefore, the average cost of PCHE administered per patient in group 6 is more than $1,000.

In conclusion, administration of human PCHE produced a significant increases in the PCHE activity in all patients. The larger the dose, the greater was the resultant plasma activity. Human PCHE produced a dose-dependent antagonism of mivacurium-induced neuromuscular blockade. The recovery times correlated inversely with PCHE activity. This study also demonstrated that, during thiopental/fentanyl/nitrous oxide/isoflurane anesthesia, administration of PCHE equivalent to activity present in 25 ml/kg of human plasma (in a 65-kg patient, this dose is equivalent to PCHE activity of 1,625 ml of adult human plasma) at 10% recovery of the first twitch height from mivacurium-induced blockade, resulted in recovery of TOF ratio to 0.75 in less than 10 min. Nevertheless, because of the prohibitive cost of this compound, this reversal modality is unlikely to have a major clinical application at this time.

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