Antagonism of Mivacurium Neuromuscular Block: Neostigmine Versus Edrophonium

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This study was designed to compare the effectiveness of antagonism of mivacurium blockade with either neostigmine, edrophonium, or spontaneous recovery. Thirty ASA physical status I or II patients provided informed consent and were randomized to one of the following groups: Group 1, placebo saline; Group 2, edrophonium (1 mg/kg); and Group 3, neostigmine (70 μg/kg) (n = 10/group). All studied patients had anesthesia induced with propofol and maintained with propofol/N_2O/fentanyl. Mivacurium bolus of 0.2 mg/kg was used for endotracheal intubation and an infusion titrated to maintain deep levels of block (T_1% = 1%–5%) (T_1 % = first response/control response × 100). The antagonist was injected at a deep level of the block (T_1 % = 1%–8%) and neuromuscular (NM) recovery was evaluated by train-of-four twitches (TOF). T_1 % was used during maintenance, whereas both T_1 % and TOF% (fourth response/first response × 100) were used during recovery. Investigators were blinded to the antagonist used. Plasma cholinesterase activity was measured prior to antagonist administration (0 min), as well as 15, 30, and 60 min after. Plasma cholinesterase activity was decreased to 29% of control at 15 min and remained at approximately 60% of the control after neostigmine administration. Edrophonium did not affect plasma cholinesterase activity. Clinically adequate spontaneous recovery (TOF% ≥ 70%) of the mivacurium block with placebo required 15–18 min. On average, clinically adequate antagonism of mivacurium by edrophonium was 50% faster than placebo and 30%–40% faster than with neostigmine. In summary, the speed of antagonism with edrophonium is faster than with neostigmine when antagonizing deep mivacurium NM block. Neostigmine-induced depression of plasma cholinesterase, slower onset of action, or combination of both may explain this observation.

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Mivacurium is a bis-quaternary, benzilisoquinoline neuromuscular (NM) blocking drug with short to intermediate duration of action. It is rapidly hydrolyzed by pseudocholinesterase (1,2).

Recovery of the NM block induced with mivacurium occurs over such a short time that anticholinesterase drugs are seldom necessary (1–3). Edrophonium and neostigmine are the most commonly used anticholinesterases in clinical practice with very different effects on plasma cholinesterase that might lead to differences in their effects on a mivacurium blockade. Neostigmine causes a profound decrease in plasma cholinesterase activity, with activity reduced to 7% of control level at 1 min, 23% at 5 min, and reaching only 50%–60% of control for up to half an hour after administration (4). Edrophonium causes no significant change in this enzyme activity (5). Several studies have reported increased rate of recovery of the mivacurium NM block with both neostigmine and edrophonium as antagonists (1,2,6–11).

Because of differences in the effects of edrophonium and neostigmine on plasma cholinesterase activity, and the critical importance of plasma cholinesterase in the metabolism of mivacurium, the present study compared the quality of the antagonism of mivacurium NM block by edrophonium to that by neostigmine. A spontaneous recovery group was used as a control. Plasma cholinesterase activity was measured immediately before and during the first hour after administration of the antagonist.

Methods

Thirty adult ASA physical status I and II patients scheduled for elective procedures requiring endotracheal intubation were studied after informed consent and institutional approval. Patients with renal, liver, endocrine, or NM disease or any electrolyte abnormality, as well as patients receiving any medication

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Table 1. Demographic Data

	Placebo (n = 10)	Edrophonium (n = 10)	Neostigmine (n = 10)
Age (yr)	32.4 ± 4.6	32.5 ± 3.6	33.3 ± 3.5
Pch activity (U/mL)	3.7 ± 0.16	3.9 ± 0.27	4.05 ± 0.19
BMI (kg/m^2)	24.6 ± 0.9	24.8 ± 1.25	25.4 ± 1.1

Values are mean ± SEM.
Pch = plasma cholinesterase activity expressed as units per milliliter; BMI = body mass index = wt (kg)/body surface area (m^2).

known to affect plasma cholinesterase or NM function were excluded from the study.

Patients were premedicated with midazolam (1–2 mg intravenously [IV]) and fentanyl (0.5–1 μg/kg IV) as deemed necessary by the attending anesthesiologist. Anesthesia was induced with propofol (2–3 mg/kg) and fentanyl (2–3 μg/kg). Propofol infusion (120–200 $\mu g \cdot kg^{-1} \cdot min^{-1}$), 60% N_2O in oxygen, and intermittent fentanyl boluses were used for maintenance of anesthesia. Ventilation was controlled to maintain end-tidal CO_2 between 30 and 35 mm Hg, as measured by mass spectrometer. Nasopharyngeal temperature was kept between 34.5 and 37.0°C by surface warming and adjusting operating room temperature. After appropriate anesthetic depth was achieved, control train-of-four (TOF) twitch response was measured. Depth of the NM block was measured with twitch monitor NMT 221 (Puritan-Bennett/Datex, Tewksbury, MA). Supramaximal train-of-four (TOF) electrical stimulations (2 Hz for 2 s with pulse width of 100 μs) of the ulnar nerve at the wrist were applied and the resulting integrated electromyogram recorded. T_1 % (first response/control response × 100) and TOF% (fourth response/first response × 100) were monitored. A mivacurium bolus (0.2 mg/kg IV) was given to facilitate intubation of the trachea, and continuous mivacurium infusion was used (4–10 $\mu g \cdot kg^{-1} \cdot min^{-1}$) for intraoperative paralysis. Infusion rate was adjusted to keep the T_1 % response between 1% and 5%. At the completion of surgery, the infusion was stopped and the antagonist administered at the deep level of the block (T_1 % = 1%–8%), as soon as some recovery of the first twitch was appreciated. Anesthesia was maintained until maximum NM recovery was recorded. Recovery was considered maximal when TOF% and T_1 % reached ≥ 95% or did not show further improvement over at least 5 min of observation. Control twitch height (twitch prior to mivacurium administration) was used to calculate T_1 % and additional calculations or adjustments of T_1 % were not performed during the recovery period. TOF% ≥ 70% was considered as clinically adequate recovery. For antagonism of NM block, the patients were randomly assigned to one of the three groups. Group 1 received neostigmine (70 μg/kg) with atropine (20 μg/kg), Group 2 received edrophonium (1 mg/kg) with atropine (15 μg/kg), and Group 3 had normal saline placebo. Solutions were prepared by the pharmacist and investigators were blinded to the type of the antagonist that the patient received. Because bradycardia (heart rate between 45 and 50 bpm with stable blood pressure) was noted in two of the first three patients in the neostigmine group, the atropine dose in the antagonist solution was increased by the pharmacy from 20 to 30 μg/kg without breaking the randomization code.

Venous blood samples for plasma cholinesterase activity measurements were obtained immediately prior to administration of the antagonist (control), as well as 15, 30, and 60 min after. Whole blood was collected using EDTA as anticoagulant and plasma separated within less than 2 h. Plasma samples were immediately frozen to −70°C and measurements of the plasma cholinesterase activity performed on all samples together. The enzymatic method using propionylthiocholine as a substrate was performed at Smith & Klein Laboratories (Chicago, IL) with the normal range for males of 2.4–6.2 U/mL and 1.7–7.4 μ/mL for females. The assay is sensitive to 0.1 U/mL and has a coefficient of variation 1.0%–1.38% at the normal range of concentrations (Dr. J. Devine, Smith & Klein Laboratories, personal communication).

Differences among groups were evaluated using the analysis of variance with Scheffe's test. Within each group, differences in plasma cholinesterase activity over time were determined by analysis of variance for repeated measures. The χ^2 test was used to evaluate demographics of the patients. Data were expressed as mean ± SEM. Statistical significance was accepted when $P < 0.05$.

Results

All patients were ASA physical status I or II, with similar age, body mass index, and sex distribution among the groups (Table 1). Scheduled surgical procedures were not extensive and did not result in major fluid shifts. There was no difference in the twitch height among the three groups at the baseline, prior to administration of the study drugs. NM block at the time of antagonism was deep with the mean value in all three groups between 4% and 6% (range 1%–8%, Table 2). There was no relationship between the depth of the block at the time of antagonist administration and the rate of recovery. Maximum recovery (T_1 %

Table 2. Single Twitch Height (%) Prior to Antagonist Administration and Maximum Recovery of the Single Twitch (T_1 %) and Train-of-Four Ratio (TOF %)

	Placebo (n = 10)	Edrophonium (n = 10)	Neostigmine (n = 10)
T_1 % preantagonist (%)	5.9 ± 0.9	4.2 ± 1.1	4.3 ± 1
T_1 % max (%)	80 ± 2.9	81 ± 2.9	75 ± 1.5
TOF max (%)	91 ± 1.7	94 ± 2.6	87 ± 2.7

Values are mean ± SEM.
T_1 % = (single twitch height/control twitch height) × 100; TOF% = (fourth twitch/first twitch) × 100; T_1 % max and TOF% max = maximum recovery, when TOF% or T_1 % reached ≥ 95% or did not show further improvement over at least 5 min of observation.

max and TOF % max) was similar in all three groups (Table 2).

Edrophonium administration significantly increased the speed of recovery of the T_1 % at all measuring points (Table 3). Mean values for recovery time to T_1 25% and 75% after neostigmine administration were similar to placebo, whereas T_1 50% was reached faster in the neostigmine group than in the placebo group. Examination of the individual patient's values revealed a large variability in the results achieved with neostigmine which was not so prominent in the remaining two groups (see SEM in Table 3).

Recovery time to TOF% of 25%, 50%, and 70% was measured. Edrophonium provided significantly faster antagonism than placebo at all measuring points, shortening the time to full clinical recovery (TOF ≥ 70%) by half when compared to placebo (8 min vs 15.8 min, Table 4). The neostigmine group recovery times to TOF 25% and 50% were shorter than placebo, but the time required for clinically adequate recovery (TOF 70%) was not different. Recovery time to TOF 25% in the neostigmine group was longer compared to the edrophonium group, but the remaining two measurements (TOF 50% and 70%) were not different between the antagonists (Table 4).

Plasma cholinesterase activity was measured during the first hour after antagonist administration and the results are reported in Figure 1. Baseline values (immediately before the administration of the antagonist solutions) were all within normal limits and not different between the groups. Enzyme activity decreased to 29.4% at 15 min after neostigmine administration and remained at 57% and 60% of control at 30 and 60 min, respectively. Edrophonium did not affect plasma cholinesterase activity at any measuring point and values measured were not different from the placebo group (Figure 1).

Discussion

Mivacurium is a short-acting, nondepolarizing relaxant with relatively rapid spontaneous recovery. The results of this study demonstrate that edrophonium is a reliable antagonist of a deep mivacurium NM block. The speed of recovery with edrophonium was more rapid than that of placebo or neostigmine. Neostigmine antagonism was variable; some patients had faster recovery, and in others the time required to reach a clinically adequate level of recovery (TOF% ≥ 70%) was similar to placebo.

Plasma cholinesterase activity was consistently suppressed during the first hour after neostigmine administration, similar to study reported by Mirakhur et al. (4). Hart et al. (12) and Mirakhur (5) demonstrated that edrophonium does not inhibit plasma cholinesterase activity. Results of plasma cholinesterase activity measurement in our study confirmed these findings. *In vitro* study of mivacurium metabolism by Cook et al. (13) showed that neostigmine, but not edrophonium, inhibits metabolism of the mivacurium in a dose-dependent fashion. In the clinical portion of the same study, neostigmine and edrophonium were equally effective antagonists, leading the authors to conclude that neostigmine is a more potent inhibitor of the true cholinesterase than the plasma cholinesterase (13). Savarese et al. (1) noted that neostigmine accelerates recovery of mivacurium block by only 40% and questioned the clinical significance of this change. Kao et al. (14) suggested that neostigmine may even delay complete recovery, when administered to patients with deep NM block. However, several other studies indicate that neostigmine accelerates antagonism of mivacurium block by 7–9 min versus spontaneous recovery that averaged 15–17 minutes (8,9). This held true even in patients with renal failure (15).

There are two ways to investigate antagonism of the NM block. In one experimental design, relaxant administration is continued during the recovery period and subsequent recovery of the NM function is assumed to be exclusively the result of the antagonist action (12,16). The second design resembles the usual clinical practice in which administration of the relaxant is discontinued prior to administration of the antagonist. Restoration of the NM function then results from the combined effects of spontaneous recovery and chemical antagonism by anticholinesterase (9,10). We decided to follow a more clinically oriented design. Mivacurium infusion was discontinued and antagonists were administered as soon as minimal NM recovery was observed. Anesthesia was maintained

Table 3. Single Twitch (T_1 %) Recovery Times

	Placebo (n = 10)	Edrophonium (n = 10)	Neostigmine (n = 10)
Time to T_1 25% (min)	4.1 ± 0.5	0.8 ± 0.1*†	3.2 ± 0.6
Time to T_1 50% (min)	8.8 ± 1	2.2 ± 0.4*†	5.1 ± 0.6*
Time to T_1 75% (min)	13 ± 1.7	5.9 ± 0.7*†	13.4 ± 2.3

Data are given as mean ± SEM.
* Significantly different from placebo ($P < 0.05$).
† Significantly different from neostigmine ($P < 0.05$).

Table 4. Train-of-Four Ratio (TOF) Recovery Times

	Placebo (n = 10)	Edrophonium (n = 10)	Neostigmine (n = 10)
Time to TOF 25% (min)	10.1 ± 0.6	3 ± 0.8*†	4.3 ± 0.5*
Time to TOF 50% (min)	13.3 ± 0.6	6 ± 0.9*	7.5 ± 1*
Time to TOF 70% (min)	15.8 ± 0.9	8 ± 0.9*	12.5 ± 3.1

Data are given as mean ± SEM.
* Significantly different from placebo ($P < 0.05$).
† Significantly different from neostigmine ($P < 0.05$).

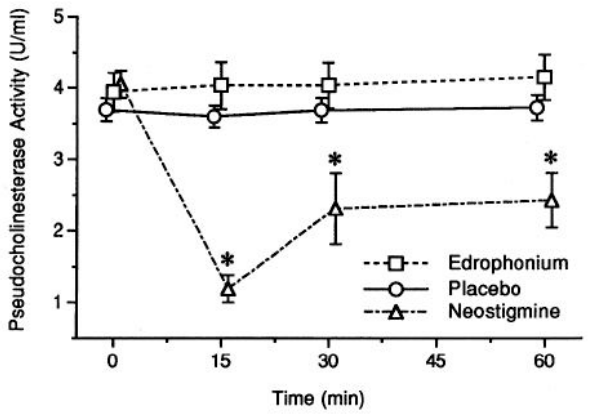

Figure 1. Plasma cholinesterase activity before (time 0) and during the first hour after antagonist administration (values are given as mean ± SE; * $P \leq 0.01$).

with propofol and N_2O to avoid any inhibitory effects of volatile anesthetics on antagonism of the NM block (17).

In our study, several measuring points suggested that mean recovery time in the neostigmine group was significantly shortened compared to the spontaneous recovery, but antagonism was unpredictable when individual recovery times were examined (see large SEM, Tables 3 and 4). The time required to reach a clinically adequate level of recovery (TOF% ≥ 70%) with neostigmine was not different from placebo (Table 4). Several studies reported an accelerated rate of the recovery of mivacurium NM block with neostigmine without the variability observed in our data (1,8,9). Timing of the antagonist administration could explain this difference. We administered the antagonist at the deep level of the block (T_1 % = 1%–8%) whereas most of the previous studies gave neostigmine when twitch recovery had reached 10% (9) or more of the control (1,8). We speculate that once recovery is well established, mivacurium NM block is relatively insensitive to changes in the plasma cholinesterase activity. At this point, potent inhibition of the true cholinesterase by neostigmine could be sufficient to provide antagonism of the mivacurium block, despite significant depression of mivacurium metabolism. In some patients in the neostigmine group recovery was slower and similar to that in the placebo group. In these patients, neostigmine may have sufficiently depressed mivacurium metabolism to markedly slow spontaneous recovery of the NM block. During the duration of the profound enzyme depression, recovery may heavily depend on antagonism. Since the peak effect of antagonism with neostigmine occurs in 7–11 min (vs 1–3 min with edrophonium) (7) neostigmine could not significantly accelerate recovery of these patients. We found that neostigmine profoundly depressed plasma cholinesterase activity, as reported by others (4,5), but we were not able to correlate the degree of depression with the speed of recovery.

Edrophonium significantly shortened the recovery time and provided reliable antagonism of the NM block in our patients. Acceleration of the recovery by 7–8 min is in accordance with results reported by others (10,11). In our study mivacurium infusion was stopped and edrophonium administered. Recovery of the NM block is then the result of both antagonism by edrophonium and spontaneous recovery. Combination of both mechanisms will provide recovery of the NM function significantly faster than spontaneous recovery alone (see placebo group in Table 4).

Edrophonium as an antagonist has several limitations. First, it has a ceiling effect when used for antagonism of the nondepolarizing NM block (16). The maximum block that can be predictably antagonized to clinically adequate levels of recovery (TOF% ≥ 70%) is lower with

edrophonium than with neostigmine (16,18). Secondly, it causes an increase in plasma concentration of mivacurium by an unknown mechanism (12). Despite these potentially important disadvantages, it has a short onset of action which gives it a very important advantage over neostigmine (1–3 min vs 7–11 min) (7,12,19). We believe that the combination of fast onset and absence of depression of plasma cholinesterase outweighs the negative effects of edrophonium, providing that mivacurium administration is discontinued before antagonism. If spontaneous recovery is combined with antagonism, edrophonium will provide significantly faster recovery than spontaneous recovery (Tables 3 and 4). Maximum recovery with edrophonium is comparable to neostigmine (Table 2).

There are several limitations of our study. First, depression of the pseudocholinesterase activity was uniformly observed after neostigmine administration, but we were not able to establish a relationship between the speed of NM recovery and the level of plasma cholinesterase activity. It is possible that enzyme activity changes prior to our first measurement at 15 min could have explained the slow antagonism of NM block with neostigmine in some of our patients. Secondly, it is possible that plasma levels of mivacurium would provide additional insight and explain individual variability in the neostigmine group. Finally, we used the highest clinically recommended doses of both antagonists to maximize speed of antagonism and effects on plasma cholinesterase activity (17). Comparison of the different doses of antagonists may give different results and diminish the advantages of edrophonium observed in our study.

In summary, our results suggest that spontaneous recovery of mivacurium NM block (placebo group) requires 15–18 min. If faster recovery of the deep NM block is desired, edrophonium, but not neostigmine, is a reliable antagonist. Neostigmine-induced inhibition of plasma cholinesterase, slow onset of action, or combination of both, could explain inconsistent effects of neostigmine on the rate of NM recovery.

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