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Edrophonium Increases Mivacurium Concentrations during Constant Mivacurium Infusion, and Large Doses Minimally Antagonize Paralysis

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Background: **Mivacurium, a nondepolarizing muscle relaxant, is metabolized by plasma cholinesterase. Although edrophonium does not alter plasma cholinesterase activity, we have observed that doses of edrophonium that antagonize paralysis from other nondepolarizing muscle relaxants are less effective with mivacurium. We speculated that edrophonium might alter metabolism of mivacurium, thereby hindering antagonism of paralysis. Accordingly, we determined the effect of edrophonium on neuromuscular function and plasma mivacurium concentrations during constant mivacurium infusion.**

Methods: **We infused mivacurium to maintain 90% depression of adductor pollicis twitch tension and then gave edrophonium in doses ranging from 125–2,000 μg/kg without altering the mivacurium infusion. Peak twitch tension after edrophonium was determined to estimate the dose of edrophonium antagonizing 50% of twitch depression for antagonism of mivacurium; plasma cholinesterase activity and mivacurium concentrations before and after edrophonium were measured. Additional subjects were given 500 μg/kg edrophonium to antagonize continuous infusions of *d*-tubocurarine and vecuronium.**

Results: **With mivacurium, edrophonium increased twitch tension in a dose-dependent manner: the dose of edrophonium antagonizing 50% of twitch depression was 2,810 μg/kg. The largest dose of edrophonium (2,000 μg/kg) produced only 45 ± 7% antagonism. Edrophonium, 500 μg/kg, antagonized mivacurium markedly less than it antagonized *d*-tubocurarine and vecuronium. Edrophonium increased plasma concentrations of the two potent stereoisomers of mivacurium 48% and 79%, these peaking at 1–2 min; plasma cholinesterase activity was unchanged.**

Conclusions: **Edrophonium doses that antagonize *d*-tubocurarine and vecuronium are less effective in antagonizing the neuromuscular effects of mivacurium during constant infusion. Edrophonium increases plasma mivacurium concentrations, partly or completely explaining its limited efficacy; the mechanism by which edrophonium increases mivacurium concentrations remains unexplained. Our results demonstrate that antagonism of mivacurium by edrophonium is impaired, and therefore we question whether edrophonium should be used to antagonize mivacurium. (Key words: Antagonists, neuromuscular: edrophonium. Enzymes, cholinesterase: plasma. Neuromuscular relaxants, nondepolarizing: mivacurium.)**

MIVACURIUM has a shorter duration of action than other nondepolarizing muscle relaxants, presumably because of its rapid clearance by plasma cholinesterase.[1] However, in certain instances, spontaneous recovery from mivacurium is sufficiently slow that a neuromuscular antagonist (*e.g.,* edrophonium) is required. In the clinical setting, we have occasionally observed incomplete or delayed antagonism by 0.5–1.0 mg/kg edrophonium. In that edrophonium is reported not to alter plasma cholinesterase activity[2] or the degradation of mivacurium *in vitro,*# this observation was unexpected. However, little is known about the dose–response relation for edrophonium antagonism of mivacurium and whether edrophonium alters mivacurium concentrations *in vivo.* Accordingly, we determined the dose–response relation for edrophonium-induced antagonism of mivacurium and whether edrophonium

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Cook DR, Chakravorti S, Brandom BW, Stiller RL: Effects of neostigmine, edrophonium, and succinylcholine on the *in vitro* metabolism of mivacurium: Clinical correlates (abstract). ANESTHESIOLOGY 77:A948, 1992.

altered mivacurium concentrations during constant mivacurium infusion.

Materials and Methods

With approval of our local Institutional Review Board and after obtaining informed consent, we studied 25 American Society of Anesthesiologists physical status 1 and 2 patients, 18–52 yr old, scheduled for elective surgery. Patients exceeding 130% of ideal body weight, those with renal, hepatic, neuromuscular, and/or electrolyte disorders, or those taking medication known to interfere with neuromuscular function were excluded.

After 1–2 mg intravenous midazolam, anesthesia was induced with 3–4 μg/kg intravenous fentanyl and 2–3 mg/kg intravenous propofol. Tracheal intubation was performed without neuromuscular blockade[3] and ventilation was controlled to maintain normocapnia (end-tidal carbon dioxide tension 30–35 mmHg). Anesthesia was maintained with 70% nitrous oxide and 1% end-tidal isoflurane (Datex Ultima, Helsinki, Finland). Cardiac rhythm (by electrocardiography), hemoglobin oxygen saturation (by pulse oximetry), blood pressure (noninvasively), and esophageal temperature were monitored continuously. Esophageal temperature was maintained at 35.5–37.0°C.

After induction of anesthesia, the ulnar nerve was stimulated *via* subcutaneous needle electrodes at the wrist. Supramaximal stimuli of 0.2-ms duration were delivered in a train-of-four at 2 Hz every 12 s (Digistim II, Neuro Technology, Houston, TX). Preload was maintained at 200–400 g. The evoked twitch tension of the adductor pollicis muscle was measured using a calibrated force transducer (Myotrace, Houston, TX) and amplified (DC Bridge Signal Conditioner, Gould Electronics, Valley View, OH). Twitch tension was then digitized (NB-M10-16, National Instruments, Austin, TX), displayed (LabView, National Instruments), and recorded on line. In addition, a strip chart recorded the evoked twitch tension (TA240, Gould Electronics). Before muscle relaxant administration, end-tidal isoflurane concentration was stable for more than 20 min and the first twitch response of each train was stable for more than 10 min (the control twitch tension).

For 17 subjects, mivacurium was infused at 1–3 $\mu g \cdot kg^{-1} \cdot min^{-1}$. When twitch tension stabilized, the mivacurium infusion rate was adjusted based on the Hill equation, targeting 90% twitch depression. When twitch tension had been stable at approximately 10% of the control value for more than 10 min and the mivacurium infusion rate had remained unchanged for more than 15 min, patients received atropine (10 μg/kg, not to exceed 1 mg) and edrophonium. The mivacurium infusion was continued unchanged throughout the remainder of the study. Patients were randomly allocated to receive one of four edrophonium doses (125, 250, 500, or 1,000 μg/kg). When an initial study demonstrated minimal effect of 125 μg/kg edrophonium, that dose was replaced with 2,000 μg/kg for subsequent studies. Thus, 1 patient received 125 μg/kg edrophonium, and 16 received 250–2,000 μg/kg (4 for each dose).

Venous blood samples (two aliquots of 5 ml each) were obtained before edrophonium (two samples separated by 10 min) and 1, 2, 4, and 8 min after edrophonium. One aliquot was used to determine plasma cholinesterase activity and dibucaine inhibition (SmithKline Beecham Clinical Laboratories, Van Nuys, CA), the other to determine mivacurium concentrations. To prevent mivacurium from degrading *in vitro,* 1.25 mg Phospholine Iodide (Wyeth-Ayerst, Philadelphia, PA) in 100 μl water was added to these samples immediately; samples were iced within 1 min and separated and frozen within 1 h. Plasma cholinesterase activity was determined photometrically using acetylthiocholine as a substrate. Mivacurium concentrations were determined by high-pressure liquid chromatography using a modification of the technique described by Brown *et al.*[4] and a spectrofluorometric detector (RF-511PC, Shimadzu, Tokyo, Japan). The assay is sensitive to 5 ng/ml for each of the three stereoisomers and has a coefficient of variation less than or equal to 16% at that concentration; the assay is not affected by the presence of edrophonium.

The remaining eight subjects received the identical anesthetic and neuromuscular monitoring as described earlier except that *d*-tubocurarine (*d*Tc) (n = 4) or vecuronium (n = 4) was infused to maintain 90% twitch depression. Atropine (10 μg/kg, not to exceed 1 mg), and 500 μg/kg edrophonium were then given, and the infusion was continued unchanged. Plasma samples (5 ml each) were obtained to determine vecuronium (but not *d*Tc) concentrations before and 1, 2, and 4 min after edrophonium. Vecuronium concentrations were determined by gas–liquid chromatography, sensitive to 10 ng/ml with a coefficient of variation less than 15% at that concentration[5]; the assay is not affected by the presence of edrophonium.

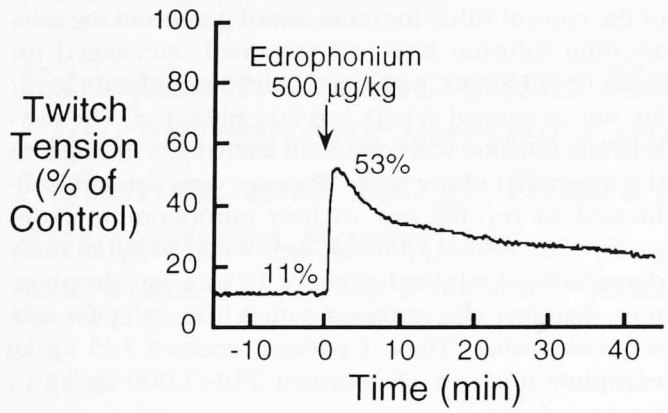

Fig. 1. Effect of 500 μg/kg edrophonium on twitch tension during constant infusion of mivacurium. Twitch tension stabilized at 11% of control before edrophonium, increased to 53% less than 2 min after edrophonium and then slowly returned toward baseline.

Peak twitch tension after antagonism and time to peak antagonism were determined. Antagonism was then calculated as:

$$\text{Antagonism} = \frac{(\text{peak twitch tension after antagonism} - \text{baseline})}{(100\% - \text{baseline})}$$

where baseline is the twitch tension immediately before edrophonium administration. For example, if twitch tension recovered from 11% of control to 53% of control, antagonism was (53% − 11%)/(100% − 11%) = 47% (fig. 1). The dose of edrophonium antagonizing 50% of twitch depression for antagonism of mivacurium was determined by linear regression of antagonism *versus* log dose. In addition, the effect of 500 μg/kg edrophonium in antagonizing mivacurium, *d*Tc, and vecuronium was compared using analysis of variance and Dunnett's test.

To document that concentrations of each of the mivacurium stereoisomers were at steady state before edrophonium administration, the two plasma concentrations obtained before edrophonium were compared using Student's *t* test for paired data. Mivacurium concentrations after edrophonium were compared with the average of the two control values using repeated measures analysis of variance. Peak mivacurium concentrations after edrophonium were determined; the percentage increase in peak mivacurium isomer concentrations after edrophonium was compared with edrophonium dose by analysis of linear regression. Plasma cholinesterase values after edrophonium were compared with control values using repeated measures analysis of variance. Plasma vecuronium concentrations were analyzed in a manner similar to that for mivacurium. Values are reported as mean ± SD. Statistical significance was accepted when $P < 0.05$.

Results

With mivacurium, twitch tension immediately before edrophonium administration was 9.6 ± 1.4%. The mivacurium infusion rates to maintain steady state 90% twitch depression ranged from 1.3–5.0 $\mu g \cdot kg^{-1} min^{-1}$ ($2.8 \pm 1.1\ \mu g \cdot kg^{-1} \cdot min^{-1}$). Concentrations of each of the mivacurium stereoisomers did not vary before edrophonium administration. Baseline plasma cholinesterase activity and values for dibucaine inhibition were normal for all subjects. Values for plasma cholinesterase activity after edrophonium were obtained in only 14 of 17 subjects because of technical difficulties with blood sampling. In these 14 subjects, edrophonium did not alter plasma cholinesterase activity (fig. 2).

With mivacurium, time to peak antagonism was less than 2 min for all patients. Antagonism increased with increasing dose of edrophonium (fig. 3, $P < 0.001$). Edrophonium, 2,000 μg/kg, produced 45 ± 7% antagonism. The dose of edrophonium antagonizing 50% of twitch depression for antagonism of mivacurium was 2,810 μg/kg (a value exceeding our largest dose of edrophonium). With *d*Tc and vecuronium, twitch tension immediately before edrophonium was 9.5 ± 1.4% and 9.5 ± 1.0%, respectively. After 500 μg/kg edrophonium, antagonism was less with mivacurium (37

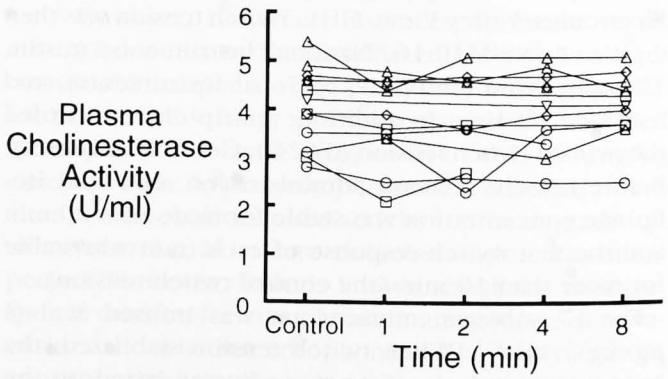

Fig. 2. Values for plasma cholinesterase activity before and after 125–2,000 μg/kg edrophonium antagonism of mivacurium.

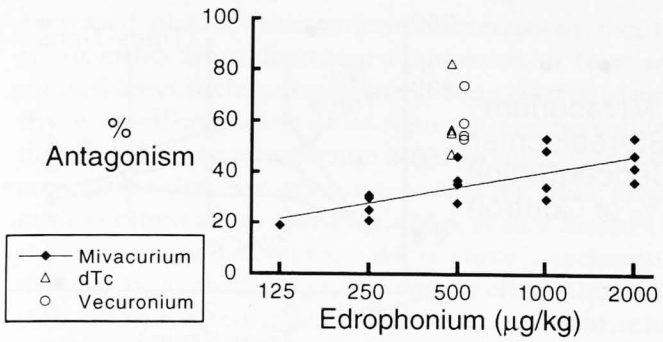

Fig. 3. The dose–response relation for edrophonium antagonism of mivacurium (diamonds and line). Values for antagonism of *d*TC (triangles) and vecuronium (circles) by 500 μg/kg edrophonium are also shown (offset laterally for clarity).

± 7%) than with *d*Tc (61 ± 15%) or vecuronium (60 ± 10%).

Plasma mivacurium concentrations were obtained in only 14 of 17 subjects (no data for two subjects given 500 μg/kg edrophonium and one given 2,000 μg/kg edrophonium). Concentrations of each of the three stereoisomers increased after edrophonium in most subjects (fig. 4); the magnitude of the peak increase did not correlate with edrophonium dose. The *trans–trans* and *cis–trans* isomers peaked at 1–2 min and declined slowly thereafter (fig. 5). The *cis–cis* isomer increased slowly and remained relatively constant between 1 and 8 min. Vecuronium concentrations did not change before or after edrophonium (166 ± 52 ng/ml before edrophonium, 169 ± 54 ng/ml at 1 min, 164 ± 52 ng/ml at 2 min, 168 ± 57 ng/ml at 4 min).

Discussion

Antagonism of a constant infusion of mivacurium by edrophonium appears to be less effective than antagonism of *d*Tc or vecuronium. This finding is consistent with our clinical observations that 0.5–1.0 mg/kg edrophonium may not effectively antagonize paralysis induced by mivacurium. Our protocol was similar to that used to examine the dose–response relation for antagonism of *d*Tc by edrophonium,[6] neostigmine,[7] and pyridostigmine.[7] In those studies, *d*Tc was infused to 90% steady-state block, after which single bolus doses of the antagonist were administered and the infusion was continued unchanged. Using this approach, Cronnelly *et al.*[6] demonstrated that the dose of edrophonium antagonizing 50% of twitch depression by *d*Tc was 128 μg/kg, a value less than one-tenth that in the current study. In addition, Cronnelly *et al.*'s[6] dose–response relation for edrophonium antagonism of *d*Tc was steeper than ours for antagonism of mivacurium ($P < 0.001$ by analysis of covariance). Although their study design differs from ours (they gave single twitches at 0.1 Hz rather than train-of-four stimuli and administered halothane rather than isoflurane), the effect of

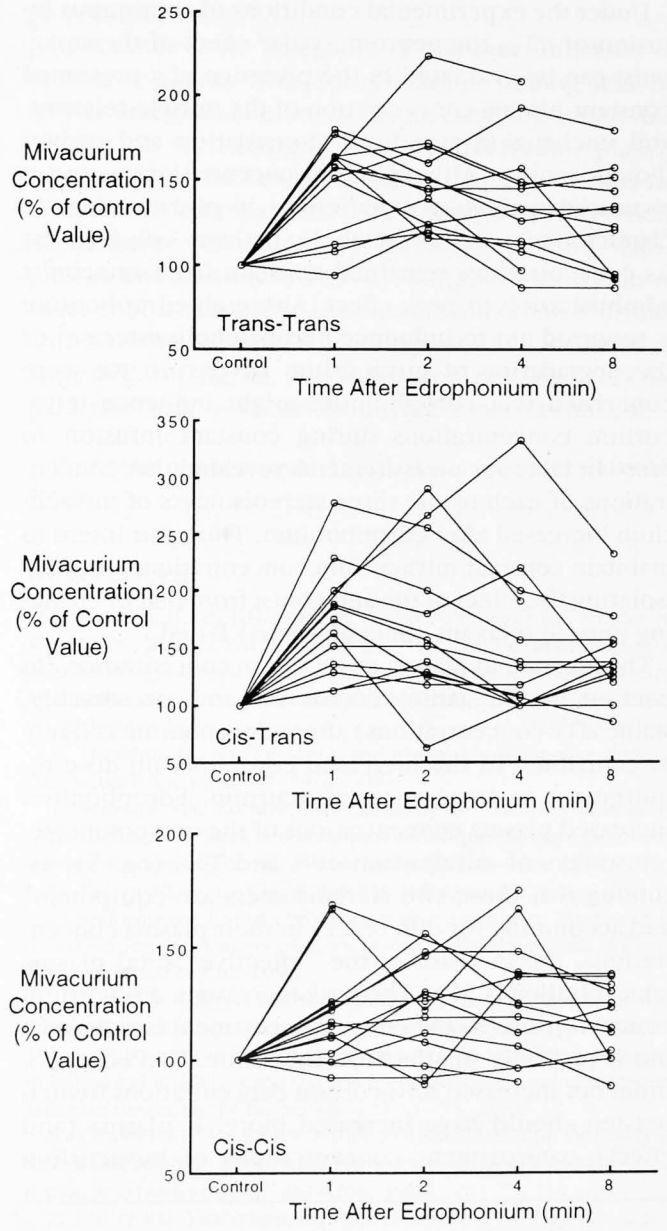

Fig. 4. Concentrations of the three stereoisomers of mivacurium for each individual before and 1, 2, 4, and 8 min after edrophonium antagonism. Values are normalized to the plasma concentration before edrophonium.

500 μg/kg edrophonium to antagonize *d*Tc is similar in the two studies (61 ± 15% *vs.* 82 ± 12%, respectively, $P > 0.05$), suggesting that comparison between our mivacurium and Cronnelly *et al.*'s[6] *d*Tc data is justified. Combined with the results from the current study, Cronnelly *et al.*'s findings suggest that antagonism of continuously infused mivacurium by edrophonium is impaired compared with antagonism of continuously infused *d*Tc or vecuronium.

Under the experimental conditions of continuous infusion of *d*Tc, the neuromuscular effect of the antagonist can be evaluated in the presence of a presumed constant plasma concentration of the muscle relaxant, and unchanging anesthetic potentiation and carbon dioxide tension. Although *d*Tc concentrations were not measured in previous experiments, its pharmacokinetic characteristics and its metabolic pathways suggest that its concentrations remained constant from antagonist administration to peak effect. Although edrophonium is reported not to influence plasma cholinesterase[2] or the degradation of mivacurium *in vitro,*# we were concerned that edrophonium might influence mivacurium concentrations during constant infusion *in vivo.* In fact, our measurements revealed that concentrations of each of the three stereoisomers of mivacurium increased after edrophonium. Thus, our intent to maintain constant mivacurium concentrations (thereby isolating the effect of the antagonist from that of changing muscle relaxant concentrations) failed.

The increase in plasma mivacurium concentration (in contrast to the stable vecuronium and, presumably, stable *d*Tc concentrations) after edrophonium is likely to contribute to the increased edrophonium dose requirement to antagonize mivacurium. Edrophonium increased plasma concentrations of the two potent stereoisomers of mivacurium 48% and 79% (fig. 5). Assuming that these two stereoisomers are equipotent[8] and accounting for differences in their plasma concentrations, the increase in the "effective" total plasma concentration is 55%. The peak increase in mivacurium concentrations in the effect compartment is unknown but is probably smaller than this value. Had edrophonium not increased mivacurium concentrations, twitch tension should have increased more. If plasma (and effect) compartment concentrations of mivacurium

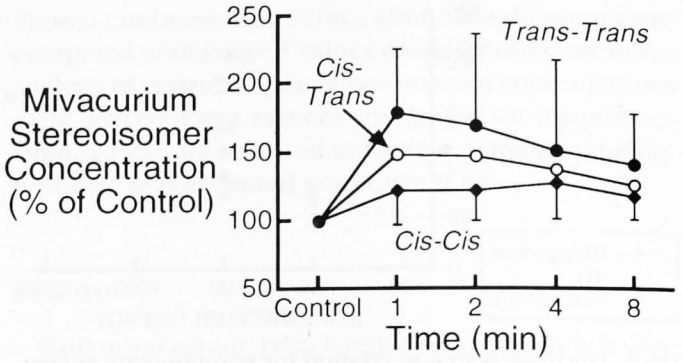

Fig. 5. Concentrations of the three stereoisomers of mivacurium before and 1, 2, 4, and 8 min after edrophonium antagonism. Values are means and SD for each stereoisomer and are normalized to the plasma concentration before edrophonium. Standard deviations for the *cis–trans* isomer (omitted for clarity) are similar to those for the *trans–trans* isomer.

were unchanged by edrophonium, we estimate (appendix) that twitch tension would have increased to 74%, corresponding to 71% antagonism.** This 71% value is similar to that for antagonism of both vecuronium and *d*Tc (60% and 61%, respectively). If the increase in effect site concentrations were less than 55%, the 71% value is an overestimate. These calculations suggest that the decreased response to edrophonium to antagonize mivacurium results, at least partially, from edrophonium's effect on mivacurium concentrations.

The peak increase in plasma mivacurium concentration was not related to edrophonium dose. Therefore, we expected that the dose–response relation for edrophonium-induced antagonism of mivacurium should have differed in position but not in slope from Cronnelly *et al.*'s values for *d*Tc[6] (whereas both slope and position actually differed). In that our largest dose of edrophonium, 2,000 μg/kg, produced less than 50% antagonism of mivacurium, the linear relation between edrophonium dose and antagonism (fig. 3) might suggest that larger edrophonium doses (exceeding 2,000 μg/kg) would effectively antagonize mivacurium during constant infusion. However, Yost and Maestrone[9] recently demonstrated that edrophonium in clinically relevant concentrations may inhibit antagonism of muscle relaxants. Perhaps this explains the difference in the slope of the dose–response relations for edrophonium-induced antagonism of mivacurium and *d*Tc: that is, increasing doses of edrophonium both inhibit and facilitate antagonism.

We are unable to explain why mivacurium concentrations increased after edrophonium administration.

** This assumes that effect compartment concentrations increased in proportion to plasma concentrations (55%) and that the 37% antagonism produced by edrophonium, 500 μg/kg, occurred despite this 55% increase in effect compartment mivacurium concentrations.

Increased plasma mivacurium concentrations should result either from decreased elimination or from increased input such as displacement of mivacurium from tissue. Based on Cook *et al.*'s# report that edrophonium did not influence mivacurium degradation *in vitro,* we anticipated that edrophonium would not alter mivacurium elimination. However, Cook *et al.*# measured the slope of the mivacurium decay curve, a technique that may be less sensitive to changes in elimination rate than measuring concentrations during constant infusion. In addition, their measurements were performed *in vitro* whereas ours were *in vivo*. Our mivacurium concentrations increased after edrophonium despite no change in plasma cholinesterase activity. Perhaps other cholinesterases or esterases contribute to the elimination of mivacurium, and these enzymes may be inhibited by edrophonium. In support of altered metabolism (rather than displacement from sites within the body) explaining the rapid increase in mivacurium concentrations is the difference in the time course of the concentration changes for the three stereoisomers: the two isomers with elimination half-lives less than 2-min[8] peaked early, whereas the *cis–cis* isomer (which has a 53-min elimination half-life[8]) peaked later.

Naguib *et al.*[10] have examined edrophonium's effects in antagonizing bolus doses of mivacurium. When twitch tension had recovered to 10% of control, some subjects were allowed to recover spontaneously and others were given 100–1,000 μg/kg edrophonium, and the time course of twitch tension recovery was compared. Although edrophonium facilitated recovery in a dose-dependent manner, Naguib *et al.*'s[10] study design did not permit them to assess the relative contribution of edrophonium and spontaneous degradation of mivacurium to the eventual recovery.

Whether edrophonium (or another antagonist such as neostigmine) should be given to antagonize mivacurium remains controversial. During initial clinical evaluation of mivacurium, there were no clinical trials to examine its antagonism from profound degrees of neuromuscular blockade, a situation common to many muscle relaxants. Despite minimal data regarding appropriate antagonist doses or the time course of antagonism, Savarese†† proposed edrophonium as the optimal antagonist for mivacurium. In contrast, Pollard[11] and Diefenbach *et al.*[12] suggested that spontaneous recovery was preferable. Our study does not identify the preferred antagonist for mivacurium or the optimal dose. In addition, our study design—continuing the infusion of the muscle relaxant after administration of edrophonium—differs from usual clinical practice, thereby limiting the clinical utility of our results. However, we demonstrate that edrophonium antagonism of mivacurium (administered by continuous infusion) is impaired compared with antagonism of *d*Tc or vecuronium.

In summary, we antagonized constant infusions of muscle relaxants with edrophonium, finding less effective antagonism of mivacurium compared with that of *d*Tc or vecuronium. After edrophonium, plasma mivacurium (but not vecuronium) concentrations increased, at least partially explaining this difference. Mivacurium concentrations increased despite stable plasma cholinesterase activity, suggesting the role of other cholinesterases in the elimination of mivacurium. Our findings suggest that edrophonium, in doses as large as 2,000 μg/kg, fails to antagonize adequately the paralysis from mivacurium during constant infusion.

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Appendix: Determination of the Effect of Increasing Muscle Relaxant Concentrations On Antagonism by Edrophonium

Using the Hill equation, twitch depression (effect) can be described as:

$$\text{effect} = \frac{Ce^{\gamma}}{Ce^{\gamma} + Ce_{50}{}^{\gamma}} \quad (1)$$

where Ce is the muscle relaxant concentration in the effect compartment; γ is the Hill coefficient; and Ce_{50} is the effect site concentration depressing twitch tension 50%. Equation A1 can be rewritten as:

$$Ce_{50}{}^{\gamma} = Ce^{\gamma} \times \left(\frac{1 - \text{effect}}{\text{effect}}\right) \quad (2)$$

If $Ce_{unchanged}$ is the effect compartment concentration if edrophonium did not alter mivacurium concentrations and $Ce_{changed}$ is the peak effect compartment concentration after edrophonium, then:

$$Ce_{50}{}^{\gamma} = Ce_{unchanged}{}^{\gamma} \times \left(\frac{1 - \text{effect}_{unchanged}}{\text{effect}_{unchanged}}\right) \quad (3)$$

$$Ce_{50}{}^{\gamma} = Ce_{changed}{}^{\gamma} \times \left(\frac{1 - \text{effect}_{changed}}{\text{effect}_{changed}}\right) \quad (4)$$

where $\text{effect}_{unchanged}$ and $\text{effect}_{changed}$ are the effects associated with the $Ce_{unchanged}$ and $Ce_{changed}$, respectively. If the right sides of equations A3 and A4 are equated, $\text{effect}_{unchanged}$ can be determined as:

$$\text{effect}_{unchanged} = \frac{1}{\left(1 + \left[\frac{Ce_{changed}}{Ce_{unchanged}}\right]^{\gamma} \times \left[\frac{1 - \text{effect}_{changed}}{\text{effect}_{changed}}\right]\right)}. \quad (5)$$

Although γ is unknown, we assume a value of 3.‡‡

At steady state, plasma concentration and Ce are proportional; after edrophonium, however, the acute increase in plasma concentration may not be matched by a comparable increase in Ce. Therefore, the impact of altered mivacurium concentration may be less than that predicted from plasma concentration measurements.

‡‡ Fisher DM: Unpublished data. 1994.