

## Edrophonium: Duration of Action and Atropine Requirement in Humans during Halothane Anesthesia

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Edrophonium's onset and duration of antagonism ( $n = 26$ ) and atropine requirement ( $n = 24$ ) were determined under conditions of *d*-tubocurarine (*d*Tc) neuromuscular blockade and halothane, nitrous oxide anesthesia. Results are compared with previous work in our laboratory on neostigmine and pyridostigmine under similar conditions. *d*Tc was administered by continuous infusion to maintain a 90% depression of muscle twitch tension. Edrophonium (0.03–1.0 mg/kg) was injected as an iv bolus in combination with atropine (0.5 mg). *d*Tc infusion was continued until a stable 90% depression of muscle twitch tension was reestablished. Time-to-peak effect (onset of action), duration, and magnitude of antagonism were recorded. The atropine requirement was determined during spontaneous recovery from *d*Tc (0.3 mg/kg) and stable halothane, nitrous oxide anesthesia. Edrophonium (0.5 mg/kg) was mixed with 7, 15, or 30  $\mu$ g/kg of atropine and compared to neostigmine (0.043 mg/kg) and atropine (15  $\mu$ g/kg). Blood pressure, heart rate, and rhythm were recorded for 60 min following edrophonium administration. The time-to-peak antagonism for edrophonium (0.8–2.0 min) was far more rapid than neostigmine (7–11 min) or pyridostigmine (12–16 min). The ED<sub>50</sub> for edrophonium was 0.125 mg/kg, however, the dose-response curve was not parallel to those for neostigmine or pyridostigmine. In equiantagonistic doses, the duration of antagonism by edrophonium (66 min) did not differ from neostigmine (76 min), but was shorter than pyridostigmine. Edrophonium required one-half the amount of atropine as did neostigmine to prevent bradycardia. The authors concluded that edrophonium has a more rapid onset than neostigmine and an equivalent duration of antagonism, and requires less atropine to prevent bradycardia. (Key words: Antagonist, neuromuscular relaxants: edrophonium; neostigmine; pyridostigmine. Measurement technique: neuromuscular blockade. Monitoring: stimulator, nerve. Neuromuscular relaxants: *d*-tubocurarine.)

EDROPHONIUM (Tensilon®), a reversible inhibitor of acetylcholinesterase, has not been used as an antagonist of nondepolarizing blockade because of its supposed brief duration of antagonism and the possibility of recurarization.<sup>1–6</sup> However, using 0.5 to 1.0 mg/kg of edrophonium, effective and sustained antagonism of both pancuronium and *d*-tubocurarine neuromuscular blockade has been demonstrated recently.<sup>7,8</sup>

However, the actual duration of antagonism produced by edrophonium has not been established. Evidence from pharmacokinetic analysis demonstrates that edrophonium does not differ from neostigmine and pyridostig-

mine in terms of elimination half-lives, distribution volumes, or clearance rates.<sup>9,10</sup> Thus, edrophonium may be expected to produce antagonism with a duration approximating that of neostigmine or pyridostigmine. To determine this, we studied the duration of action of edrophonium during continuous infusion of *d*-tubocurarine at stable anesthetic concentrations.

To prevent bradycardia that results from the use of anticholinesterase drugs as antagonists, atropine or other anticholinergics must also be given. This combination has been associated with tachycardia and other dysrhythmias of atrial, nodal, and ventricular origin.<sup>11–14</sup> The antagonist requiring the least amount of atropine may decrease the tachycardia and possibly the frequency of other dysrhythmias. Studies in animals suggest that edrophonium has less muscarinic activity than neostigmine.<sup>15,16</sup> However, the dose of atropine required to prevent bradycardia during antagonism of neuromuscular blockade with edrophonium has not been determined. Therefore, we also compared the atropine requirements of equiantagonistic doses of edrophonium and neostigmine in terms of changes in heart rate, mean arterial pressure, and frequency of dysrhythmias.

### Methods

The protocol was approved by our Committee on Human Research. Informed consent was obtained from 26 surgical patients ASA Class I and II. All patients had normal laboratory values for serum electrolytes, BUN, creatinine, SGOT, and alkaline phosphatase. About one hour following the oral administration of diazepam (10 mg), anesthesia was induced with thiopental (2–4 mg/kg) and maintained with nitrous oxide 60% inspired and halothane 0.4–0.7% end-tidal concentration as measured by mass spectrometer. Endotracheal intubation was accomplished without the use of muscle relaxants. Normal blood gases (PaCO<sub>2</sub> 35–40 mmHg) and body temperatures (34–36°C esophageal) were maintained. Supramaximal square-wave pulses of 0.15-ms duration at 0.15 Hz were delivered to the ulnar nerve at the wrist through 27-gauge needle electrodes. The resultant force of thumb adduction was quantified with a Grass FT<sub>10</sub> force displacement transducer and recorded on a polygraph. *d*-Tubocurarine was administered as an intravenous bolus and then infused at a rate sufficient to maintain 90% depression of twitch tension. Adjustment of the infusion rate was required during the first 30 to 60 min following which a stable level of neuromuscular blockade resulted,

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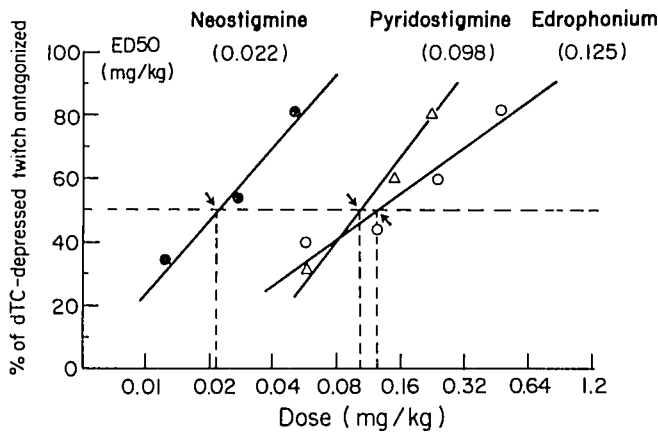


FIG. 1. Comparison of dose response and ED<sub>50</sub> for neostigmine, pyridostigmine, and edrophonium. Values plotted are means and the lines determined by analysis of linear regression. Values for neostigmine and pyridostigmine are replotted from the data of Miller.<sup>19</sup> Edrophonium 0.5 mg/kg was equiantagonistic to neostigmine (0.043 mg/kg) or pyridostigmine (0.22 mg/kg).

and the infusion was continued at this rate. After at least 20 min of stable 90% blockade, edrophonium in doses of 0.03 mg/kg (n = 3), 0.06 mg/kg (n = 5), 0.125 mg/kg (n = 5), 0.25 mg/kg (n = 5), 0.5 mg/kg (n = 5), or 1 mg/kg (n = 3) was injected as a rapid intravenous bolus combined with 0.5 mg atropine. Antagonism of twitch depression was determined as a percentage of the preexisting 90% depression. (e.g., control twitch height was 50 mm depressed to 5 mm by dTc, i.e., a 90% depression. If peak twitch height after edrophonium was 30 mm, then the 5-mm twitch height remaining after the dTc was subtracted 30 - 5/50 - 5 or 56% of the dTc depressed twitch was antagonized by edrophonium). In addition, we measured the time required for twitch tension to increase to 50% of peak (17.5 mm in the example) and to peak antagonism (onset of action), and to decrease

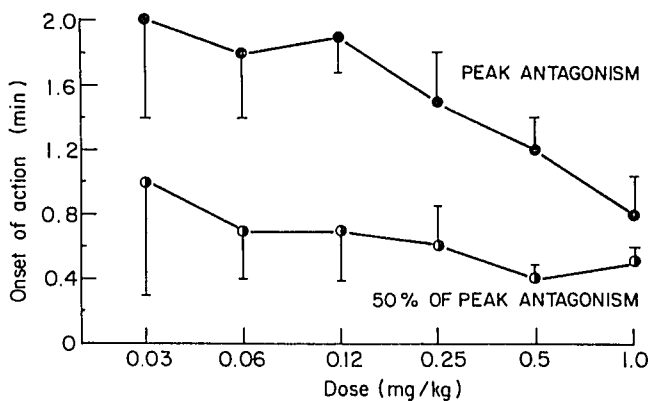


FIG. 2. Onset of action for edrophonium. Values plotted are means  $\pm$  SE. The onset of edrophonium's action was extremely rapid, even in low doses (0.03 mg/kg).

to 30% (12.5 mm in the example) of peak effect (duration of action).

An additional 24 adult surgical patients, ASA Class I and II with normal preoperative electrocardiograms were selected to determine the atropine requirement for edrophonium. Anesthesia was administered as described previously. dTc (0.3 mg/kg) was administered intravenously and the response monitored by observing the train-of-four (T<sub>4</sub>). When recovery of two of the four twitches in the T<sub>4</sub> occurred, the neuromuscular blockade was antagonized with either edrophonium (0.5 mg/kg) or neostigmine (0.043 mg/kg). Neostigmine was mixed with its optimum dose of atropine (15  $\mu$ g/kg) as determined previously,<sup>17</sup> while edrophonium was randomly mixed with one of three doses of atropine (7, 15, or 30  $\mu$ g/kg). Measurements of blood pressure (using Dinamap blood pressure monitor), heart rate, and rhythm (polygraph recording of EKG, lead II) were made at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, and 60 min following antagonist administration.

Data were analyzed by linear regression, analysis of variance, and chi-square test. Differences were considered significant at  $P < 0.05$ .<sup>18</sup>

### Results

The results obtained in this study are compared with previous work in our laboratory on neostigmine and pyridostigmine under similar conditions.<sup>19</sup>

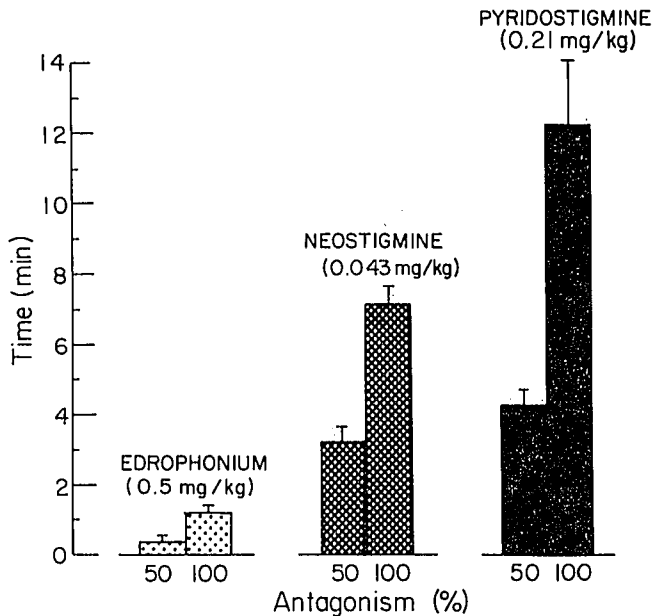


FIG. 3. Comparison of onset of action for edrophonium, neostigmine, and pyridostigmine. Values plotted are means  $\pm$  SE, those for neostigmine and pyridostigmine are replotted from the data of Miller.<sup>19</sup> Edrophonium's onset was significantly faster than neostigmine or pyridostigmine.

The dose of edrophonium that produced 50% antagonism of *d*Tc depressed twitch ( $ED_{50}$ ) was 0.125 mg/kg. However, the dose-response curve was not parallel to those of neostigmine and pyridostigmine (fig. 1). Since responses to the 1 mg/kg and 0.03 mg/kg doses did not fall on the linear portion (*i.e.*, between 20 to 80% response) of the dose-response curve they were not included in the  $ED_{50}$  determination. A dose of 1 mg/kg ( $n = 3$ ) produced  $100 \pm 0\%$  antagonism (mean  $\pm$  SE), while 0.03 mg/kg produced  $12 \pm 5\%$  antagonism ( $n = 3$ ). Edrophonium, 0.5 mg/kg, was found equiantagonistic to neostigmine 0.043 mg/kg and pyridostigmine 0.21 mg/kg (fig. 1). The onset of action of edrophonium (*i.e.*, time from drug administration to peak antagonism) was extremely rapid over the entire dose range (fig. 2), and was significantly faster than neostigmine or pyridostigmine at equiantagonistic doses (fig. 3). Dose-dependent increase in the duration of antagonism occurred up to a dose of 0.125 mg/kg, above which no further increase could be produced (fig. 4). At equiantagonistic doses the duration of edrophonium's antagonism did not differ from neostigmine (fig. 5). The duration of both drugs, however, was significantly less than with pyridostigmine.

Compared to neostigmine (0.043 mg/kg) and atropine (15  $\mu$ g/kg), the simultaneous administration of edrophonium (0.5 mg/kg) and atropine (7  $\mu$ g/kg) resulted in minimal changes in heart rate or MAP (figs. 6 and 7). Higher doses of atropine combined with edrophonium resulted in prolonged tachycardia (fig. 8) and elevations in MAP. The incidence of dysrhythmias was not related to the atropine dose and occurred as frequently with edrophonium (0.5 mg/kg) and atropine (7  $\mu$ g/kg) as

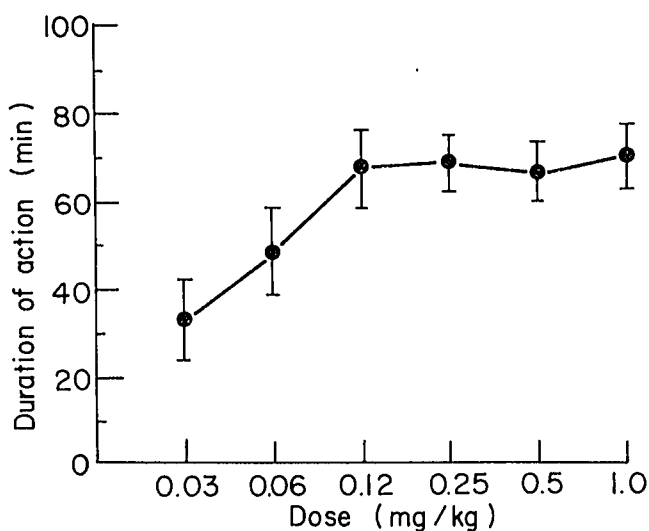


FIG. 4. Duration of action of edrophonium. Values plotted are means  $\pm$  SE. Duration of the response increased up to a dose of 0.125 mg/kg, after which no further increase occurred in spite of an 8-fold increase in dose.

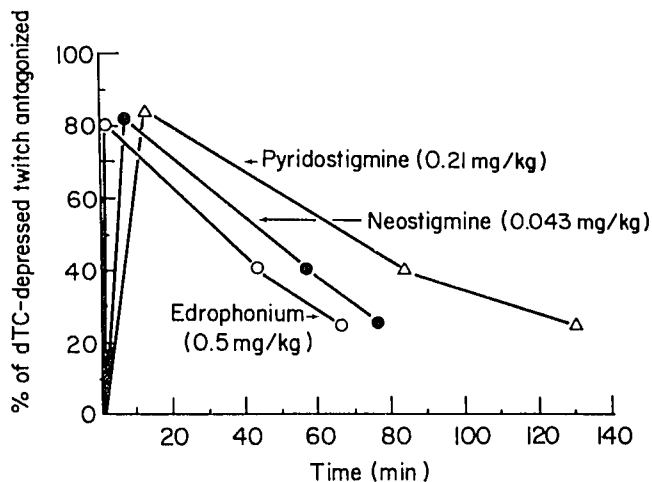


FIG. 5. Duration of antagonism compared at equipotent doses of neostigmine, pyridostigmine, and edrophonium. Values plotted are means and those for neostigmine and pyridostigmine are replotted from the data of Miller.<sup>19</sup> Edrophonium did not differ from neostigmine in duration, however, both were shorter than pyridostigmine.

with neostigmine (0.043 mg/kg) and atropine (15  $\mu$ g/kg) (table 1).

### Discussion

Antagonism of a *d*-tubocurarine neuromuscular blockade by edrophonium was of rapid onset and long duration over a wide range of doses. In addition, edrophonium required less atropine to prevent bradycardia than an equiantagonistic dose of neostigmine. In this study, the

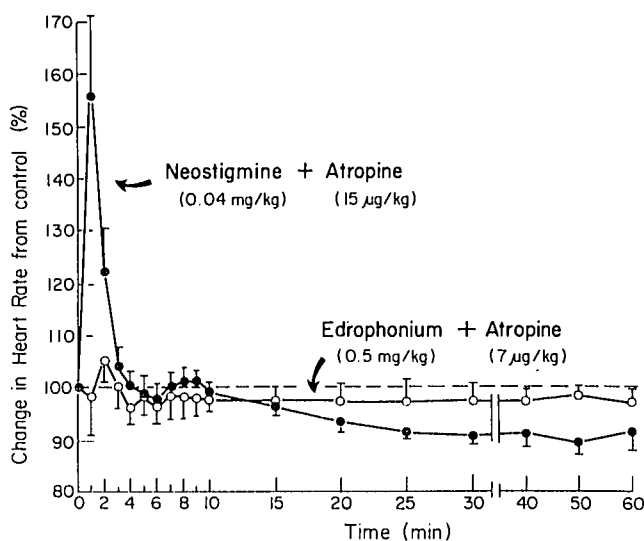


FIG. 6. Atropine requirement for equipotent doses of neostigmine and edrophonium. Values are means  $\pm$  SE for changes in heart rate plotted as a per cent of control. Compared to neostigmine and atropine, the simultaneous administration of edrophonium and atropine produced minimal changes in heart rate.

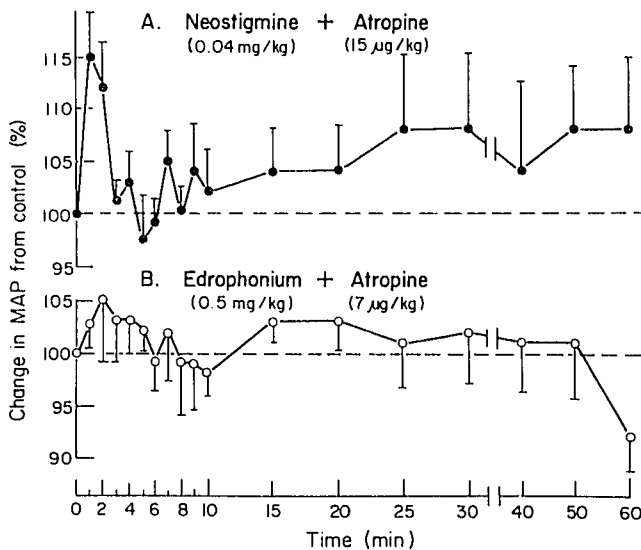


FIG. 7. Comparison of changes in mean arterial pressure following equipotent doses of neostigmine and edrophonium mixed with atropine 15  $\mu\text{g}/\text{kg}$  and 7  $\mu\text{g}/\text{kg}$ , respectively. Values plotted are means  $\pm$  SE. When mixed with atropine, edrophonium produced minimal changes in MAP compared to neostigmine.

effect of the antagonist was superimposed on a constant level of neuromuscular blockade and anesthetic concentration. This approach allowed a more accurate definition of the effect due to the antagonist drug alone. We were also able to compare these results to an identical study in our laboratory using neostigmine and pyridostigmine.<sup>19</sup>

Comparing antagonist potency at a dose producing 50% antagonism ( $\text{ED}_{50}$ ), neostigmine was 4.4 times more

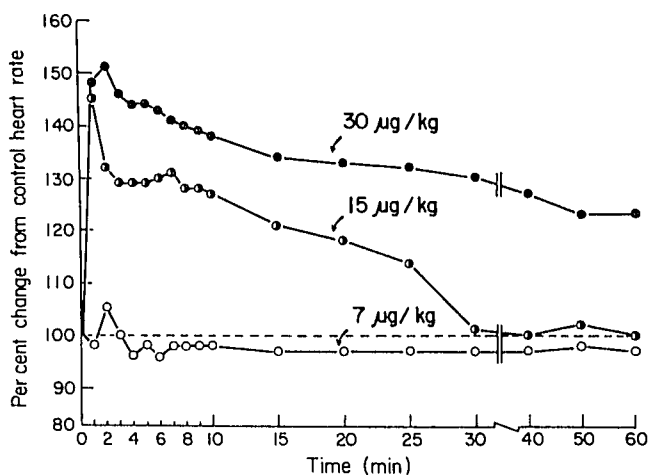


FIG. 8. Change in heart rate following administration of edrophonium (0.5 mg/kg) mixed with atropine 7 (n = 5), 15 (n = 7), or 30  $\mu\text{g}/\text{kg}$  (n = 5). Values plotted are means. Doses of atropine higher than 7  $\mu\text{g}/\text{kg}$  produce prolonged tachycardia.

TABLE 1. Type and Frequency of Dysrhythmias

Drug Combination	Frequency	Type
0.5 mg/kg edrophonium + 30 $\mu\text{g}/\text{kg}$ atropine	1/5 (20%)	Nodal
0.5 mg/kg edrophonium + 15 $\mu\text{g}/\text{kg}$ atropine	4/7 (57%)	Nodal
0.5 mg/kg edrophonium + 7 $\mu\text{g}/\text{kg}$ atropine	2/5 (40%)	Atrial + Nodal
0.043 mg/kg neostigmine + 15 $\mu\text{g}/\text{kg}$ atropine	2/7 (30%)	Nodal

potent than pyridostigmine and 5.7 times more potent than edrophonium. However, the dose-response curve for edrophonium is not parallel to those of neostigmine and pyridostigmine and therefore, the potency ratio is misleading. Potency ratios would vary depending on what point on the dose-response curve is used to make the comparisons, *i.e.*,  $\text{ED}_{25}$ ,  $\text{ED}_{50}$  (dashed vertical lines in fig. 1), or  $\text{ED}_{75}$ . The dose of edrophonium equian-tagonistic to the common clinical dose of neostigmine (0.043 mg/kg) or pyridostigmine (0.21 mg/kg) was 0.5 mg/kg. Differences in potency between the drugs cannot be explained on a pharmacokinetic basis since neostigmine, pyridostigmine, and edrophonium have similar distribution volumes.<sup>9,10</sup> Affinity for the acetylcholinesterase enzyme is probably of major importance in determining relative potency as an inhibitor,<sup>20</sup> and also may govern potency at other sites of action thus contributing to the dose requirements of the antagonists. Perhaps of greater significance is the fact that the edrophonium dose-response curve is not parallel to those for neostigmine and pyridostigmine. This suggests that different mechanisms may be involved in the antagonism produced by edrophonium.

The time to peak antagonism (onset of action) for edrophonium (0.8–2.0 min) was more rapid than that found for neostigmine (7–11 min) or pyridostigmine (12–16 min).<sup>19</sup> Drug distribution times do not account for differences in onset of action since the  $t_{1/2\alpha}$  for edrophonium (7.2 min) and pyridostigmine (6.8 min) are similar.<sup>9,10</sup> Onset differences may reflect times required for enzyme inhibition. Under *in vitro* conditions, in the absence of acetylcholine, Wilson<sup>21</sup> calculated that a concentration of neostigmine inhibiting 90% of a given amount of acetylcholinesterase would produce 45% inhibition in one minute, compared with 2.8 s for edrophonium. Although the time required for significant inhibition may be longer *in vivo*, under competitive con-

ditions with acetylcholine it may explain the faster onset for edrophonium. Alternatively, different mechanisms with faster time constants may also explain the more rapid onset of antagonism with edrophonium compared to neostigmine.

Several differences have been found in the mechanism of action of edrophonium as compared to neostigmine and pyridostigmine. Since the structure of edrophonium does not contain a carbamate group, its binding to acetylcholinesterase is easily reversible and transient. Carbamylation of the esteratic site by neostigmine and pyridostigmine produces a longer lasting inhibition.<sup>21,22</sup> In addition, direct stimulation of the end-plate region has not been found to contribute to the anticholinergic action of edrophonium as it has for neostigmine.<sup>23,24</sup> Miniature end-plate potential frequency, quantal release, size, and rate of the available acetylcholine store are increased by edrophonium and neostigmine at concentrations that do not prolong the end-plate potential.<sup>25-28</sup> Therefore, the effects of these drugs on the nerve terminal do not appear to result from inhibition of cholinesterase with acetylcholine as the mediator. Edrophonium appears to have predominantly presynaptic effects which may explain differences in dose-response relationships and onset of action as compared to neostigmine and pyridostigmine.

Edrophonium (0.5 mg/kg) produced antagonism with a duration which did not differ from that achieved by neostigmine but was less than that of pyridostigmine.<sup>19</sup> The magnitude of antagonism produced by edrophonium increased with dose; however, the duration of antagonism only demonstrated this relationship at doses below 0.125 mg/kg (fig. 4). This is unusual since a maximum duration response would not be expected to occur at a dose at which the magnitude of antagonism is much less than maximum. If the duration of antagonism was directly proportional to the duration of enzyme inhibition, then the greater blood levels produced as the dose of edrophonium increases should continue to lengthen the time of inhibition and therefore antagonism. The results we obtained are inconsistent with this premise. Based on previous pharmacokinetic studies,<sup>9,10</sup> it is also difficult to assume that blood levels from the administration of 2-4 mg/70 kg (0.03-0.06 mg/kg) of edrophonium are maintained at a concentration sufficient to competitively inhibit acetylcholinesterase resulting in antagonism of 30-50 min duration (fig. 4). Although our evidence is indirect, it suggests that the duration of antagonism may be independent of acetylcholinesterase inhibition and of the blood levels of edrophonium.

Equipotent doses of neostigmine and pyridostigmine required equal amounts of atropine to prevent bradycardia associated with their administration.<sup>17</sup> In a dose

equipotent to neostigmine (0.043 mg/kg), edrophonium required half the amount of atropine to prevent bradycardia and minimize the tachycardic response. Cholinergic (muscarinic) stimulation of the heart produces bradycardia, while tachycardia occurs due to the slower onset of action of neostigmine or pyridostigmine relative to atropine. The reduced muscarinic stimulant capacity of edrophonium and its faster onset of action may reduce the variation in heart rate.

The association of dysrhythmias such as inverted P waves, Wenchebach phenomena, premature atrial contractions, junctional rhythms, A-V dissociation, premature ventricular contractions, and bigeminy with the anticholinesterase drug or its combination with atropine is not clear.<sup>11-14</sup> Many of these studies were performed during emergence from anesthesia when changing levels of surgical stimulation and ventilation may have caused the dysrhythmias. However, dysrhythmias occurred even when we held these variables constant. Although our series is small, edrophonium (0.5 mg/kg) in combination with atropine (7 µg/kg) produced atrial and junctional dysrhythmias at a frequency which did not differ statistically from neostigmine (0.043 mg/kg) and atropine (15 µg/kg). Ventricular or other dysrhythmias were not observed. The dysrhythmias were unrelated to atropine dose, were of brief duration, and were not associated with significant changes in mean arterial pressure.

Since the duration of antagonism by edrophonium is equal to that of neostigmine, the more rapid onset of edrophonium's action coupled with minimal changes in heart rate may prove clinically advantageous.

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