

# Recovery Times Following Edrophonium and Neostigmine Reversal of Pancuronium, Atracurium, and Vecuronium Steady-state Infusions

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The ability of edrophonium and neostigmine to antagonize nondepolarizing neuromuscular blockade produced by steady-state infusions of atracurium, pancuronium, and vecuronium was studied in 71 adult patients anesthetized with nitrous oxide and halothane. Infusion rates of blocking drugs were adjusted so that single twitch depression as measured by the evoked integrated EMG of the hypotenar muscles was kept at 10% of control. Two minutes after the termination of the infusion either edrophonium (0.75 mg/kg) or neostigmine (0.05 mg/kg) was administered. Single twitch depression and train-of-four (T4/T1) fade was recorded during the recovery period. T4/T1 fade ratios observed at 20 min postreversal were 0.80 (atracurium-edrophonium); 0.76 (vecuronium-edrophonium); 0.44 (pancuronium-edrophonium); 0.95 (atracurium-neostigmine); 0.89 (vecuronium-neostigmine); and 0.68 (pancuronium-neostigmine). Under conditions of this study neostigmine produced more rapid and complete recovery than did edrophonium. Although edrophonium produced adequate antagonism of atracurium if 20-30 min were allowed to elapse, edrophonium reversal of pancuronium was rarely acceptable even at 30 min. Increasing the dose of edrophonium to 1.0 mg/kg produced single twitch values of 0.90 at 5 min postreversal but did not increase the rate of recovery of the train-of-four fade ratio. Neostigmine reversal of pancuronium, on the other hand, generally produced T4/T1 ratios of >0.70 in 20-30 min. Although the pattern of recovery seen after reversal of vecuronium was in general quite similar to that seen after atracurium, two patients in the vecuronium-edrophonium group showed delayed recovery and also failed to respond significantly to subsequent doses of neostigmine. Following steady-state infusions of vecuronium, it appears that marked patient variability in the speed of recovery can occur. Our results do not confirm other published reports that suggest that edrophonium and neostigmine may be used interchangeably. (Key words: Monitoring; neuromuscular blockade. Neuromuscular antagonists: edrophonium; neostigmine. Neuromuscular relaxants: atracurium; pancuronium; vecuronium.)

This article is accompanied by an Editorial. Please see Miller RD: Are studies of neuromuscular blocking drugs and their antagonists unnecessarily confusing? ANESTHESIOLOGY 65:569-571, 1986.

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Received from the Department of Anesthesiology, Long Island Jewish Medical Center, State University of New York School of Medicine at Stony Brook, Long Island, New York. Accepted for publication July 3, 1986.

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IT IS GENERALLY accepted that the speed and extent of reversal from nondepolarizing neuromuscular blockade is influenced by the magnitude of preexisting block, and that prompt and complete antagonism of profound paralysis may be difficult to achieve. Published data, however, as to what represents a level of twitch depression incompatible with early and adequate recovery are frequently contradictory. Katz<sup>1</sup> demonstrated that return of single twitch height (T1/Tc) to >0.95 might take as long as 30 min if T1/Tc was less than 20% of control when antagonism of a pancuronium-induced blockade (bolus) with neostigmine was attempted. The train-of-four fade ratio (T4/T1) was not examined. Ferguson *et al.*<sup>2</sup> using various doses of either neostigmine, edrophonium, or pyridostigmine, also attempted to reverse pancuronium administered by single bolus when T1/Tc had returned to 0.10. The authors were able to achieve T1/Tc and T4/T1 values of >0.90 and 0.75, respectively, at 30 min with any one of six reversal protocols. In addition, they attained essentially complete reversal of block in as little as 10 min if high doses of neostigmine or edrophonium were employed.

Cronnelly *et al.*,<sup>3</sup> on the other hand, using a steady-state infusion of *d*-tubocurarine at T1/Tc levels of 0.1, were unable to achieve better than 80% reversal of single twitch depression with equipotent doses of any of the earlier mentioned anticholinesterases (neostigmine 0.043 mg/kg, edrophonium 0.50 mg/kg, or pyridostigmine 0.21 mg/kg). T4/T1 fade was not studied by these authors.

It is apparent, therefore, that the ability to antagonize satisfactorily nondepolarizing neuromuscular block is, in addition to the degree of preexisting block, also a function of the experimental model employed. While reversal of 90% twitch depression during recovery from a single ED<sub>95</sub> bolus of blocking drug may be readily achieved, antagonism of similar degrees of block during steady-state infusions may be incomplete or require quite large doses of anticholinesterases at best.

Unfortunately, neither of these models accurately reflects the clinical situation that exists following multiple bolus administration during long surgical procedures. The steady-state infusion model has little relevance to actual clinical practice because antagonists are not administered during continued delivery of the blocking drug. Recovery

following the single bolus model, however, does not produce the slower plasma decay curves that may exist following prolonged drug administration of the longer-acting relaxants such as pancuronium and *d*-tubocurarine. I therefore studied the ability to antagonize 90% twitch depression produced by nondepolarizing blocking drugs using a model that may more closely mimic a "worst-case" clinical situation.

### Methods

Seventy-one adult ASA I-II patients undergoing elective surgical procedures, for whom the administration of a muscle relaxant was indicated by the proposed surgery, were included in the study. The protocol was approved by our hospital's Human Subject Review Committee. Anesthesia was induced with thiamylal sodium and maintained with nitrous oxide and halothane (0.50% inspired) plus narcotic supplementation as needed. Body temperature was maintained at  $>35^{\circ}\text{C}$ .

The indirectly evoked integrated compound action potential (EMG) of the hypothenar muscles to supramaximal stimulation of the ulnar nerve was measured and recorded using a Datex™ 221 NMT monitor. After anesthesia was induced and before any relaxants were administered, control T1/Tc and T4/T1 values were established. Train-of-four stimulation was given every 20 s during the period of observation, and single twitch depression and train-of-four fade were continuously recorded. Patients were assigned to one of seven groups.

**Group 1, Atracurium-Edrophonium ( $n = 11$ ).** Atracurium 0.3 mg/kg was administered as a bolus iv. When twitch depression was maximal, the patient's trachea was intubated, and an infusion of atracurium ( $6\ \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) was begun. The infusion was then adjusted to provide  $90 \pm 5\%$  depression of T1/Tc for the remainder of the case. Only patients in whom the infusion requirements were stable for at least 20 min prior to antagonism were included in the study. The duration of all infusions exceeded 90 min. At the end of the surgical procedures the infusion was stopped. Two minutes later edrophonium 0.75 mg/kg was given as an iv bolus. T1/Tc and T4/T1 were recorded for 20 min. If T4/T1 was  $<0.80$  at this time, additional doses of 0.25 mg/kg were given until this value was reached.

**Group 2, Atracurium-Neostigmine ( $n = 10$ ).** Protocol in this group was identical to Group 1 except that antagonism was produced with neostigmine 0.05 mg/kg.

**Group 3, Pancuronium-Edrophonium ( $n = 10$ ).** Protocol in this group was identical that in Group 1 except that the bolus of relaxant was pancuronium 0.05 mg/kg, and the initial infusion consisted of pancuronium  $0.3\ \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ . In addition the observation period post-reversal was not less than 30 min.

TABLE 1. Level of Statistical Significance of Observed Differences (*P*)

Comparison	T1/Tc 5 min	T4/T1 5 min	T1/Tc 20 min	T4/T1 20 min
AE vs. AN	NS	NS	NS	$<0.05$
PE vs. PN	$<0.05$	NS	NS	$<0.01$
VE vs. VN	NS	NS	NS	NS
AN vs. PN	$<0.01$	NS	NS	$<0.01$
AE vs. PE	NS	NS	NS	$<0.01$
AE vs. VE	NS	NS	NS	NS
AN vs. VN	NS	$<0.05$	NS	NS
PE vs. PE(HD)	$<0.05$	NS	NS	NS

NS = not significant; A = atracurium; V = vecuronium; P = pancuronium; E = edrophonium; N = neostigmine; E(HD) = high dose edrophonium.

**Group 4, Pancuronium-Neostigmine ( $n = 9$ ).** Protocol was identical to Group 3 except that reversal was induced with neostigmine 0.05 mg/kg.

**Group 5, Vecuronium-Edrophonium ( $n = 13$ ).** Protocol was identical to Group 1 except that initial bolus of drug was vecuronium 0.05 mg/kg, and the initial rate of infusion was  $1.0\ \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ .

**Group 6, Vecuronium-Neostigmine ( $n = 10$ ).** Protocol was identical to Group 5, except that antagonism was produced with neostigmine 0.05 mg/kg.

**Group 7, Pancuronium-High-dose Edrophonium ( $n = 8$ ).** Protocol was identical to Group 3, except that the dose of edrophonium was 1.0 mg/kg.

The rates of recovery of T1/Tc and T4/T1 at 5 and 20 min postantagonism were tested by one-way analysis of variance. Eight pair-wise comparisons were then made using the Student-Newman-Keuls test for multiple comparisons: Group 1 versus 2, Group 3 versus 4, Group 5 versus 6, Group 2 versus 4, Group 1 versus 3, Group 1 versus 5, Group 2 versus 6, and Group 3 versus Group 7. Observed differences were considered significant when  $P = <0.05$  (table 1).

### Results

#### GROUPS 1 (ATRACURIUM-EDROPHONIUM) AND 3 (PANCURONIUM-EDROPHONIUM)

The extent of blockade at the time reversal was attempted was similar in the atracurium and the pancuronium groups (T1/Tc of 0.107 and 0.113, respectively), as was the duration of the infusions in these two groups ( $137\ \text{min} \pm 14\ \text{SEM}$  and  $142\ \text{min} \pm 15\ \text{SEM}$ ). The pattern of recovery following edrophonium administration was also quite similar in both groups for the first 3 to 5 min ( $P > 0.05$ ). There was an immediate and striking improvement in the value of T1/Tc with the reappearance of a measurable T4/T1 ratio. This initial rapid rate of augmentation in twitch height and T4/T1 ratio was complete

TABLE 2. Single Twitch Depression from Time of Administration of Anticholinesterase and for 20–30 Min Thereafter

Group No.	T1/Tc (±SD)—Time Postreversal (min)			
	0	5	20	30
1—AE (n = 11)	0.107 (0.023)	0.709 (0.083)	0.886 (0.051)	—
2—AN (n = 10)	0.109 (0.016)	0.77 (0.13)	0.95 (0.07)	—
3—PE (n = 10)	0.113 (0.024)	0.74 (0.10)	0.81 (0.11)	0.83 (0.13)
4—PN (n = 9)	0.10 (0.04)	0.56 (0.21)	0.88 (0.13)	0.93 (0.10)
5—VE (n = 13)	0.096 (0.027)	0.83 (0.13)	0.91 (0.10)	—
6—VN (n = 10)	0.096 (0.027)	0.83 (0.06)	0.95 (0.04)	—
7—PE(HD) (n = 8)	0.096 (0.028)	0.88 (0.094)	0.92 (0.078)	0.95 (0.073)

T1/Tc = 1st twitch in train of four/control twitch; A = atracurium; P = pancuronium; V = vecuronium; E = edrophonium; N = neostigmine; HD = high dose.

in 2–3 min. At 5 min postreversal, there was little difference between Groups 1 or 3 in either T1/Tc or T4/T1 (see tables 2 and 3). In neither group was T4/T1 at 5 min indicative of adequate clinical recovery.

The rate of recovery of atracurium in the subsequent 20 min, however, was quite different from that of pancuronium ( $P < 0.01$ ). With atracurium there was always continued further improvement with time. The mean T4/T1 ratio at 20 min post-edrophonium was 0.80, and the lowest value observed at that time was 0.55. This latter value was in a 79-yr-old patient following a 4-hr infusion.

With pancuronium the rate of recovery of T4/T1 after the first 5 min was one-fourth to one-fifth that seen with atracurium. The mean T4/T1 ratios at 20 and 30 min were only 0.44 and 0.51, respectively. Three of ten patients studied in this group showed essentially no improvement in the height of the fourth twitch of the train-of-four after the first 5 min. In only one patient in the pancuronium group was T4/T1  $> 0.70$  at 30 min post-edrophonium.

#### GROUP 2 (ATRACURIUM–NEOSTIGMINE)

Recovery with this drug combination exceeded that seen in the other study groups. At 15 and 20 min postreversal mean T4/T1 ratios were 0.91 and 0.95, respectively. Only one patient had a T4/T1 value of  $< 0.80$  at 15 min. In addition, seven of ten patients had T4/T1 ratios of  $> 0.95$  at 20 min, a degree of recovery not observed in any other group.

#### GROUP 4 (PANCURONIUM–NEOSTIGMINE)

The pattern of reversal from pancuronium after neostigmine administration consisted of a phase of relatively rapid recovery followed by a period of more gradual improvement. The distinction, however, between the first and second phases of recovery was less clearly defined than following edrophonium. Generally, the initial stage of recovery was complete in 10–15 min. At 5 min post-neostigmine the T1/Tc and T4/T1 values of 0.56 and 0.25 were lower than those of Group 3 at that time interval; however, by 20–30 min postdrug administration, the T4/T1 ratios following neostigmine of 0.68 and 0.75 were greater than those achieved following the use of edrophonium ( $P < 0.05$ ). At 30 min postneostigmine only two of nine patients had T4/T1 fade ratios of  $< 0.70$  compared with nine of ten individuals in Group 3.

#### GROUP 5 (VECURONIUM–EDROPHONIUM)

The mean T1/Tc ratio at the time reversal was attempted was 0.096. Mean T1/Tc values at 5, 15, and 20 min postreversal were 0.83, 0.89, and 0.91, respectively. The mean T4/T1 at these times were 0.50, 0.70, and 0.76. The mean rate of recovery in the vecuronium group was not significantly different from that seen with atracurium ( $P > 0.05$ ). Four patients failed to attain a T4/T1 ratio  $> 0.70$  at 20 min postreversal. Of some concern, however, were two patients in the vecuronium group (see "Discussion") who showed quite slow recovery despite additional increments of neostigmine and edrophonium.

#### GROUP 6 (VECURONIUM–NEOSTIGMINE)

The mean T1/Tc ratio at the time reversal was attempted was 0.096. T1/Tc averaged 0.83 at 5 min, 0.93 at 15 min, and 0.95 at 20 min. post reversal. The rate of T4/T1 recovery as expected was slower. Values at 5, 15, and 20 minutes were 0.60, 0.84, and 0.89 respectively. All patients had T4/T1 ratios of  $> 0.70$  at 15 minutes.

#### GROUP 7 (PANCURONIUM–HIGH-DOSE EDROPHONIUM)

Increasing the dose of edrophonium to 1.0 mg/kg significantly increased the single twitch height at 5 min compared with Group 3. However, there was no difference between Groups 3 and 7 in the rate at which the T4/T1 ratio recovered. Four of eight patients had T4/T1 ratios at 30 min of  $< 0.50$ , and in two patients the value was  $> 0.40$ .

Table 1 summarizes the statistical significance of the observed differences in rates of reversal at 5 and 20 min of T1/Tc and T4/T1.

**Discussion**

It is well documented that larger doses of a nondepolarizing relaxant (at least for the traditional long-acting drugs) result in a slower rate of recovery.<sup>4</sup> For example, assume, for pancuronium, a  $T_{1/2}$  alpha of 11.2 min, a  $T_{1/2}$  beta of 107 min, clearance equal to  $1.8 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ , and a central volume of distribution of  $99 \text{ ml/kg}$ .<sup>5</sup> If the desired plasma level of drug is  $0.20 \text{ } \mu\text{g/ml}$  for a 70-kg individual, it is possible, using equations of Somogyi *et al.*,<sup>6</sup> to compare the rates of plasma decay during recovery following three different methods of administration: 1) *single bolus*—one intravenous dose of 3 mg; 2) *steady-state*—attained by administering an initial loading dose of 3.9 mg, followed by an infusion of  $1.52 \text{ mg/h}$  for 100 min; and 3) *multiple bolus administration*—an initial bolus of 3 mg plus increments of 1.0 mg whenever plasma levels fall below  $0.15 \text{ } \mu\text{g/ml}$  during a 2-h period. This protocol would require additional doses at 30, 55, and 85 min.

During recovery from a single 3.0 mg bolus, plasma levels fall from  $0.20$  to  $0.10 \text{ } \mu\text{g/ml}$  in only 30 min. Following termination of a steady-state infusion at which the plasma concentration is maintained at  $0.20 \text{ } \mu\text{g/ml}$  for 100 min, it takes 70 min for the plasma levels to decrease to  $0.10 \text{ } \mu\text{g/ml}$ . In the multiple dose model it again takes approximately 70 min for the plasma level to fall from  $0.20$  to  $0.10 \text{ } \mu\text{g/ml}$  following the last incremental dose. The close agreement in plasma decay rates between the latter two methods of administration suggests that the steady-state infusion technique is a valid model for reproducing the conditions that exist after multiple bolus administration of nondepolarizing blocking agents, even if the elapsed time of administration is as short as  $1\frac{1}{2}$ –2 h.

The levels of twitch suppression maintained during this study represent very profound blockade. At EMG  $T_1/T_c$  values of 0.10, the mechanical response is often completely suppressed.<sup>7</sup> At the outset of this investigation I was interested in two issues. Is antagonism of profound but not total paralysis more easily attained with a muscle relaxant of intermediate duration as opposed to a longer acting drug such as pancuronium? Second, is neostigmine more efficacious under these conditions than edrophonium? I felt that any differences, for example, between pancuronium and atracurium or between neostigmine and edrophonium would be more apparent if the level of paralysis was maintained just short of total blockade, because even with long-acting drugs, reversal may be quite prompt and complete following administration of edrophonium if  $T_4/T_1$  ratios are first allowed to recover to values  $>0.15$ .<sup>8</sup>

One additional point on methodology must be mentioned in several individuals  $T_1/T_c$  did not return to

TABLE 3. Train-of-four Fade Ratio from Time of Administration of Anticholinesterases and for 20–30 Min Thereafter

Group No.	T <sub>4</sub> /T <sub>1</sub> (±SD)—Time Postreversal (min)			
	T <sub>1</sub> /T <sub>c</sub> at 0	5	20	30
1—AE (n = 11)	0.107	0.398 (0.097)	0.795 (0.126)	—
2—AN (n = 10)	0.109	0.42 (0.15)	0.95 (0.06)	—
3—PE (n = 10)	0.113	0.35 (0.11)	0.44 (0.15)	0.51 (0.17)
4—PN (n = 9)	0.10	0.25 (0.14)	0.68 (0.14)	0.76 (0.13)
5—VE (n = 13)	0.096	0.50 (0.18)	0.76 (0.20)	—
6—VN (n = 10)	0.096	0.60 (0.09)	0.89 (0.06)	—
7—PE(HD) (n = 8)	0.096	0.41 (0.051)	0.48 (0.173)	0.55 (0.189)

T<sub>4</sub>/T<sub>1</sub> = train of four fade ratio; A = atracurium; P = pancuronium; V = vecuronium; E = edrophonium; N = neostigmine; HD = high dose.

100% of control despite  $T_4/T_1$  ratios as high as 1.00. In those individuals where  $T_4/T_1$  was  $>0.85$ , indicating that full recovery of  $T_1/T_c$  should have been present, the mean value of  $T_1/T_c$  was only 0.94, and a few individuals had  $T_1/T_c$  values as low as 0.85. This failure of  $T_1/T_c$  to return to baseline is a common problem with EMG recordings and is of unknown etiology. Although it is unclear if this phenomenon represents artifact or a true change in neuromuscular transmission, it should have no effect on the accuracy of  $T_4/T_1$  determinations. It is possible, however, that the  $T_1/T_c$  values that we recorded at the time of termination of our infusions may, therefore, be 5–10% too low. For example, the true mean value of  $T_1/T_c$  at time zero in Group 1 was closer to 0.12 than the reported figure of 0.107, *etc.*

*Groups 1 and 3.* At 5 min after reversal, neither the atracurium nor pancuronium blockade was acceptably antagonized by a dose of  $0.75 \text{ mg/kg}$  of edrophonium. Failure to produce adequate return of the  $T_4/T_1$  ratio with edrophonium in the presence of profound blockade is not a new observation,<sup>9</sup> and is really not unexpected because at this time drug levels at the synaptic cleft are still probably quite close to steady-state values. During recovery from a single  $ED_{95}$  dose of a blocking drug, there can be a significant gradient between the drug concentration in the plasma and at the synaptic cleft.<sup>10</sup> This gradient is nonexistent during steady-state infusions,<sup>11</sup> and it is possible that differences in reversibility between these two models may in part reflect the presence or absence of such gradients.

The similarity of atracurium and pancuronium reversal by edrophonium at 5 min was in contrast to the subsequent pattern of recovery of these two groups. With atracurium, although the rate of return of the fourth twitch was not always rapid, it was always a continuous process. From 5 to 20 min postreversal of atracurium, the rate of recovery of T4/T1 averaged about 2.5%/min and was never less than 1.7%/min. In the pancuronium group the mean rate of recovery of T4/T1 from 5 to 30 min was less than 0.6%/min, and in three patients there was essentially no further recovery in the height of the fourth twitch during this period.

Under the conditions of this study 0.75 mg/kg of edrophonium was an unreliable antagonist of pancuronium. However, when atracurium was the blocking drug, edrophonium produced mean T4/T1 values in the range of 0.80 if 15–20 min is allowed to elapse. While this is hardly prompt reversal, train-of-four ratios of this magnitude are probably adequate.<sup>12</sup> However, it should be noted that the work of Ali *et al.*, indicating that respiratory mechanics are clinically acceptable when train of four ratios exceed 0.60–0.70, was performed using mechanical twitch response rather than the evoked EMG as the parameter being measured. There is evidence that when the evoked EMG T4/T1 of the hypothenar muscles has returned to the range of 0.70–0.85, simultaneously recorded MMG twitch response of the adductor pollicis may still be below 0.6–0.7.<sup>7</sup> The precise evoked EMG response of the hypothenar muscles that represents “full clinical recovery” is not yet resolved.

While plasma levels of atracurium and pancuronium were not measured in this study, the difference in the rates of recovery is probably secondary to the quite dissimilar pharmacokinetic profiles of these two drugs. Following termination of a steady-state infusion, it takes more than an h for the plasma level of pancuronium to decrease by 50%. Atracurium plasma levels, on the other hand, will fall by this amount in less than 15 min. There is no evidence to suggest that under steady-state conditions (infusion ongoing) that atracurium is any easier to reverse than pancuronium.

*Group 2.* Neostigmine reversal of atracurium blockade resulted in T4/T1 ratios of at least 0.80 within 15 min, with the mean value at 20 min of 0.95. These results have practical clinical implications. As long as a minimal evoked response to indirect nerve stimulation is maintained during atracurium administration, prompt and complete antagonism is obtainable with 0.05 mg/kg of neostigmine, regardless of the duration of blockade.

*Groups 3 and 4.* It is difficult to reconcile our results with those of Cronnelly *et al.* during steady-state infusions.<sup>3</sup> These authors found that 0.5 mg/kg of edrophonium and 0.043 mg/kg neostigmine produced com-

parable amounts of reversal and had the same duration of action. The differences that we observed in the pattern of recovery following edrophonium and neostigmine may have been missed by Cronnelly *et al.* for two reasons. First, they did not monitor evoked train-of-four responses. Second, the continued infusion of relaxant into the postreversal period resulted in eventual return of neuromuscular blockade. While Cronnelly *et al.* investigated *d*-tubocurarine rather than pancuronium, there is no evidence to suggest that under the conditions of their study (an ongoing continuous infusion), there is any difference in ease of reversal when one neuromuscular blocker is substituted for another.

Our observations also suggest that the single-bolus model may not accurately predict the ability of anticholinesterases to reverse residual paralysis when large or multiple doses of blocking agents have been administered. For example, Breen *et al.*<sup>13</sup> using a single bolus of pancuronium (0.07 mg/kg), failed to observe any difference in the efficacy of neostigmine and edrophonium when reversing an intense blockade. These investigators found that neostigmine 0.05 mg/kg and edrophonium 0.83 mg/kg both produced T1/Tc ratios of 0.90 within 10 min postreversal when the single twitch had recovered to 10% of control. Unfortunately, the authors did not comment on the rate of return of the T4/T1 ratio. The values of T4/T1 observed during the recovery period in the present study do not support the conclusion that edrophonium is a satisfactory alternative for neostigmine when neuromuscular blockade is intense.

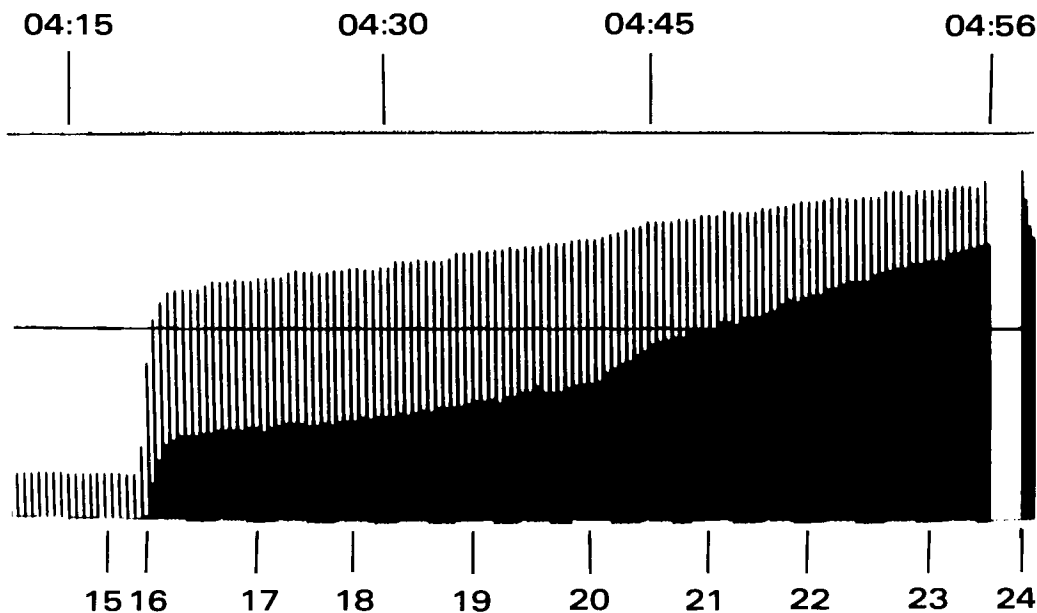
*Groups 5 and 6.* All patients in Group 6 (vecuronium–neostigmine) had T4/T1 ratios in excess of 0.75 at 20 min postreversal, and the average values in Group 5 (vecuronium–edrophonium) suggest a rapid rate of recovery. However, two patients in the vecuronium–edrophonium group gave cause for concern. The first was a 70-yr-old, ASA PS II, female (71 kg) with normal kidney and liver function tests who received a total dose of vecuronium over 4 h and 20 min of 12 mg. During the last hour, an infusion of  $0.40 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  produced a stable T1/Tc ratio of 0.11. The initial dose of 0.75 mg/kg of edrophonium resulted in T1/Tc and T4/T1 values of only 0.72 and 0.48, respectively, at 20 min postreversal. At that time 0.04 mg/kg of neostigmine was administered. Fifteen minutes later T1/Tc and T4/T1 ratios of 0.85 and 0.78 were recorded. An additional 0.15 mg/kg of edrophonium was given and 5 min later (42 min after the termination of the infusion) T1/Tc and T4/T1 ratios of 0.94 and 0.84 were achieved (fig. 1). Despite apparently normal renal and hepatic function, the low infusion rate required suggests altered elimination, which probably accounted for the increased cholinesterase required. The second case was a 67-yr-old ASA PS I female undergoing

a total abdominal hysterectomy. She weighed 67 kg. The only significant laboratory finding was a slightly elevated serum glutamic pyruvic transaminase (SGPT). The total dose of vecuronium administered was 12.5 mg over 2½ h. During the last 30 min prior to reversal, the infusion rate was stable at  $0.77 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ , and the evoked T1/Tc was 0.08. The initial dose of edrophonium produced T1/Tc and T4/T1 values of only 0.78 and 0.36 at 25 min postreversal. Following an additional 0.25 mg/kg of edrophonium, values of 0.84 and 0.50 were achieved at 30 min postreversal. Neostigmine 0.04 mg/kg was then given, and 15 min later the last recorded values for T1/Tc and T4/T1 were 0.91 and 0.70, respectively. In contrast to the first case, this patient was particularly puzzling. The mean infusion rate for all 23 patients who received vecuronium was  $0.92 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \pm 0.38 \text{ SD}$ . In this patient the infusion rate of  $0.77 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  and resulting T1/Tc ratio of 0.08 were not significantly different from our average patient under light halothane anesthesia, indicating normal clearance of the drug. Nevertheless, antagonism was slow and difficult to achieve.

**Group 7.** The dose of edrophonium (0.75 mg/kg) employed in Groups 1, 3, and 5 was chosen because it has been demonstrated that the potency ratio of neostigmine to edrophonium is between 12–16:1<sup>14,15</sup> and that the ED<sub>90</sub> for neostigmine is approximately 0.05 mg/kg.<sup>15</sup> A recent paper by Rupp *et al.*,<sup>16</sup> however, suggests that if the dose

of edrophonium is increased to 1.0 mg/kg, satisfactory antagonism of even deep levels of pancuronium-induced neuromuscular blockade is possible. In an attempt to reproduce these results, a final group (pancuronium–edrophonium 1.0 mg/kg) was added to this study. Increasing the dose of edrophonium from 0.75 to 1.0 mg/kg did result in a significant ( $P < 0.05$ ) increase in the evoked single twitch response at 5 min, which corroborates the results of Rupp *et al.* However, these authors did not investigate the rate of return of the train-of-four fade ratio. As can be seen in table 2, increasing the dose of edrophonium had no appreciable effect on the speed of recovery of this parameter. If a T4/T1 ratio of >0.60–0.70 is accepted as representing full recovery of respiratory mechanics,<sup>12</sup> then the results of this study do not support the conclusions of Rupp *et al.*, that 1.0 mg/kg of edrophonium is as effective as neostigmine in antagonizing profound neuromuscular blockade. It should be noted that the mean cumulative dose of pancuronium administered in the patients of Rupp *et al.*, was only 0.036 mg/kg. The average total dose of pancuronium in Groups 3 and 7 of this study was considerably higher (0.095 mg/kg). This difference in methodology may also explain one other observed discrepancy between this study and that of Rupp *et al.*, who suggest that neostigmine 0.04 mg/kg is capable of returning T1/Tc to levels of >0.90 within 12 min at all levels of spontaneous recovery from pan-

FIG. 1. Case no. 1 (Group 5, vecuronium–edrophonium): At marker no. 15, the infusion was turned off and edrophonium 0.75 mg/kg was administered 2 min later (no. 16). At 5 min postreversal (no. 17), T1/Tc = 0.62; T4/T1 = 0.37. At 20 min postreversal (no. 20), T1/Tc = 0.75; T4/T1 = 0.48; and neostigmine 0.43 mg/kg was administered. At 35 min (no. 23) T1/Tc = 0.85; T4/T1 = 0.78. An additional 0.15 mg/kg of edrophonium was given at this point. Five minutes later (not shown) T1/Tc = 0.94; T4/T1 = 0.84. Note that the initial slope of recovery of T4/T1 was only 0.0075/min. If neostigmine had not been given at no. 20, the projected time postreversal for return of T4/T1 to a value of >0.70 would have been at 50 min. Time from initial dose of relaxant (h:min) is at top of recording. See discussion for further details.



curonium. The results of this study suggest that using 0.05 mg/kg of neostigmine, this figure may be closer to 20–25 min.

It is apparent from our investigation that there is no simple answer to the question: What level of twitch depression is incompatible with prompt and satisfactory antagonism? Ease of reversal is a function not only of the level of paralysis, but also of the blocking drug employed, the anticholinesterase chosen, and the experimental conditions of the study.

Finally, the results of this study should not be interpreted to mean that the use of edrophonium should be abandoned. Rather, they reaffirm the importance of monitoring neuromuscular function during anesthesia. When mechanical train-of-four count is 4, edrophonium produces prompt and reliable antagonism<sup>8</sup> with fewer muscarinic side effects than neostigmine.<sup>3</sup> Rational decisions concerning which anticholinesterase to employ at the end of surgery, however, are only possible when the degree of twitch depression is known by the clinician.

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