# Edrophonium priming for antagonism of atracurium neuromuscular blockade

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*Edrophonium administered in divided doses has been reported to accelerate antagonism of neuromuscular blockade, i.e., a "priming" effect. Since measured onset times can be affected by the type of stimulation used, this effect was studied using both train-of-four (TOF) and single twitch (ST) stimulation. During thiopentone-nitrous oxide-enflurane anaesthesia 20 adults were given atracurium 0.5 mg · kg$^{-1}$. Both ulnar nerves were stimulated with TOF every 12 sec until one per cent recovery of first twitch ($T_1$). At this time, ST stimulation was applied to one arm, selected at random. When the mean value of $T_1$ and ST reached ten per cent of control, edrophonium, 1 mg · kg$^{-1}$, preceded by atropine was given either as a single dose, or in two doses consisting of 0.2 mg · kg$^{-1}$ followed by 0.8 mg · kg$^{-1}$ three minutes later. No statistically significant differences were observed between $T_1$ and ST for the next ten minutes, whether edrophonium had been given in single or divided doses. Giving edrophonium in divided doses did not improve recovery significantly, measured with either $T_1$, ST or train-of-four ratio ($T_4/T_1$). Five minutes after the first administration of edrophonium, $T_1$ was (mean ± SEM) 86 ± 3 and 86 ± 2 per cent control in the single and divided dose groups respectively. Corresponding values for ST were 89 ± 1 and 89 ± 2 per cent (NS), and for TOF, 49 ± 3 and 57 ± 3 per cent (NS), respectively. At ten minutes, values of $T_1$, ST and $T_4/T_1$ were 98 ± 1, 96 ± 1 and 64 ± 3 per cent respectively in the single dose group, not significantly different from the corresponding values in the divided group (95 ± 2, 96 ± 1 and 68 ± 3 per cent). It is concluded that giving edrophonium in divided doses, i.e., "priming" does not accelerate reversal of atracurium-induced neuromuscular blockade. Furthermore, in the assessment of edrophonium antagonism, the first twitch response to TOF stimulation is equivalent to single twitch response.*

*On a déjà décrit une neutralisation plus rapide du bloc neuromusculaire en séparant la dose d'édrophonium (un effet d'amorce). Parce que le type de stimulation peut changer la mesure de la rapidité de l'effet, on a utilisé le train-de-quatre (TDQ) et la stimulation unique (SU) simultanément. On a donné 0,5 mg · kg$^{-1}$ d'atracurium à 20 sujets adultes anesthésiés au thiopental, protoxyde d'azote et enflurane. On a stimulé en TDQ le nerf cubital de chaque côté toutes les 12 secondes. Lorsque le premier élément du TDQ ($T_1$) atteignait un pour cent, on a substitué la SU au TDQ pour un côté choisi au hasard. Lorsque la moyenne de $T_1$ et la reponse à la SU atteignait dix pour cent, on a injecté de l'edrophonium soit en une seule dose de 1,0 mg · kg$^{-1}$, soit en une dose de 0,2 mg · kg$^{-1}$ suivie, trois minutes plus tard, de 0,8 mg · kg$^{-1}$. Le $T_1$ ne s'écartait pas significativement de SU, que l'édrophonium ait été donne en une ou deux doses. L'administration d'édrophonium en deux doses ne produisait pas une meilleure récupération, que celle-ci soit mesurée en termes de $T_1$, de SU ou de rapport du TDQ ($T_4T_1$). Cinq minutes aprés la première injection d'édrophonium, le $T_1$ s'élevait à (moyenne ± ETM) 86 ± 3 et 86 ± 2 pour cent de la valeur contrôle après une dose unique et séparée, respectivement. Les valeurs correspondantes de SU étaient de 89 ± 1 et 89 ± 2 pour cent respectivement (NS). Pour le TDQ, elles étaient de 49 ± 3 et 57 ± 3 pour cent (NS) respectivement. Apres dix minutes, le $T_1$, SU et $T_4/T_1$ étaient de 98 ± 1, 96 ± 1 et 64 ± 3 pour cent respectivement chez les malades ayant reçu une dose unique, et de 95 ± 2, 96 ± 1 et 68 ± 3 pour cent les sujets ayant eu une dose séparée (différences non-significatives dans tous les cas). On en conclut que l'administration d'édrophonium en doses séparées (l'amorce) n'accelére pas la neutralisation du bloc neuromusculaire produit par l'atracurium. De plus, dans l'évaluation de l'effet de l'édrophonium, le premier élément du TDQ équivaut à la réponse à la stimulation unique.*

**Key words**

ANTAGONISTS, NEUROMUSCULAR RELAXANTS: edrophonium;
MONITORING, NEUROMUSCULAR: train-of-four, single twitch;
NEUROMUSCULAR RELAXANTS: atracurium;
PHARMACODYNAMICS: priming principle.

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Five studies have suggested that antagonism of neuromuscular blockade could be accelerated if either edrophonium or neostigmine were given in divided instead of single doses.[1-5] This "priming" effect was evaluated by measuring the time from first administration of the reversal agent until train-of-four ratio ($T_4/T_1$) became greater than 75 per cent. This effect could not be demonstrated in another study using neostigmine, during which both single twitch (ST) and train-of-four (TOF) responses were measured for at least ten minutes after the first administration of neostigmine.[6]

The type of stimulation used affects the measured onset time of neuromuscular blockade. Abolition of twitch response appeared sooner when TOF was used instead of ST for monitoring atracurium or succinylcholine block.[7] The reasons for this difference are uncertain, but it is possible that muscle blood flow is greater with TOF and thus preferential delivery of the drug and therefore a more rapid onset occurs in TOF stimulated muscle.[7] The same hypothesis was proposed to explain the effectiveness of neostigmine priming. A priming dose of the drug would produce sufficient contraction of TOF-stimulated muscle to cause preferential delivery of the second dose, i.e., an enhanced effect with priming. However, the time courses of TOF and ST responses after neostigmine administration were found to be very similar, and priming was found to be ineffective.[6] This finding may be due to the relatively slow onset of neostigmine action (5–7 min).[8] As a result, a small dose of neostigmine produces too little antagonism within 3 min to alter blood flow distribution significantly. However, edrophonium produces a more rapid antagonism.[8] Thus, it is conceivable that priming might work in this case, because a small dose of the drug produces rapid antagonism of neuromuscular blockade. As a result, TOF stimulated muscle would contract sufficiently to increase its oxygen requirement and blood flow. If this were the case, the response to ST would be less than TOF when edrophonium is given in divided doses.

To test this hypothesis, edrophonium was administered either as a single bolus dose or in divided doses. All patients received both ST and TOF stimulation.

## Methods

The protocol was approved by the Hospital Ethics Committee. Twenty adult patients, ASA physical status I or II, scheduled for elective surgery were included in the study after appropriate consent had been obtained. Patients with known or suspected renal, hepatic, or neuromuscular diseases were excluded, as were those with electrolyte abnormalities and those taking medications known or suspected to interfere with neuromuscular function.

In the operating room, ECG and pulse oximetry were monitored continuously. To minimize interference with neuromuscular recording, arterial blood pressure was monitored non-invasively with a cuff attached to the leg. Anaesthesia was induced with thiopentone, 3–5 $mg \cdot kg^{-1}$, and fentanyl, 1–2 $\mu g \cdot kg^{-1}$, and was maintained with 70 per cent nitrous oxide and one per cent end-tidal enflurane in oxygen (as measured by mass spectrometry). Both hands and forearms were immobilized in splints and the ulnar nerves were stimulated supramaximally at the elbow with square-wave pulses 0.2 ms in duration at a frequency of 2 Hz for two seconds via surface electrodes. This train-of-four (TOF) pattern was repeated every 12 sec. The forces of contraction of both adductor pollicis muscles were measured with FT-10 force transducers (Grass Medical Instruments) and recorded on paper. After a stable baseline had been obtained, atracurium, 0.5 $mg \cdot kg^{-1}$ was injected IV. Tracheal intubation was performed when twitch response was abolished. Then, the patients' lungs were mechanically ventilated and ventilation was adjusted to keep end-tidal $CO_2$, as measured by mass spectrometry, between 30 and 35 mmHg.

If recovery occurred before completion of surgery, incremental doses of atracurium, 5 mg, were given. Towards the end of the surgical procedure, when first twitch height ($T_1$) had recovered to one per cent of its control value in either arm, one arm was allocated at random to receive single twitch (ST) stimulation every 12 sec. Train-of-four stimulation to the other arm was continued. When the mean value of single twitch height in one arm and $T_1$ in the other reached ten per cent, edrophonium was given intravenously. Patients were randomly allocated to receive either edrophonium 1 $mg \cdot kg^{-1}$ in a single dose, or 0.2 $mg \cdot kg^{-1}$ followed by 0.8 $mg \cdot kg^{-1}$ three minutes later. Atropine, 0.01 $mg \cdot kg^{-1}$ was given before edrophonium administration. An additional dose of atropine was given if required. Neuromuscular monitoring was continued for at least ten minutes after the first administration of edrophonium. In the arm that otherwise received only ST stimulation, TOF stimulation was applied once at five minutes and again at ten minutes.

The values of ST, $T_1$ and $T_4/T_1$ were measured every min after first administration of edrophonium. To determine whether $T_1$ was equivalent to ST, both values were compared using analysis of variance for repeated measures. A Newman Keuls test was used whenever statistically significant differences were obtained. Similarly, the $T_4/T_1$ obtained at five and ten minutes in the arm that received ST stimulation was compared with similar values obtained in the contralateral arm. The effectiveness of priming was evaluated by comparing ST, $T_1$ and

$T_4/T_1$ from the group given edrophonium in a single dose against corresponding values from the group which received divided doses, using analysis of variance for repeated measurements. Time was counted from the first injection of edrophonium. Results are presented as means plus or minus standard error of the mean (SEM). A $P$ value less than 0.05 was considered to indicate statistically significant differences.

## Results

There were 12 males and eight females in the study. The mean age ± SEM was 43 ± 4 yr and mean weight was 66 ± 3 kg. There were no significant differences between groups with respect to sex, age or weight.

Edrophonium was first administered 83 ± 12 min after the first injection of atracurium. At that time, $T_1$ was 10.6 ± 1.0 per cent of control in the arm which received ST stimulation compared with 7.4 ± 0.5 per cent in the arm which received TOF. This small difference was present in both the single dose and the divided dose groups (Table). After three minutes, before giving the second dose in the divided dose group, recovery was greater in the single dose group (Table, Figure 1). At that time, there was less recovery of $T_1$ than ST in the divided dose group ($P < 0.05$).

Between five and ten minutes after first administration of edrophonium, no statistically significant differences were found between ST and $T_1$ responses. Also, there were no statistically significant differences between single and divided dose groups. For example, at five minutes ST was 89 ± 1 and 89 ± 2 per cent in single and divided dose groups respectively. Corresponding values for $T_1$ were 86 ± 3 and 86 ± 2 per cent, respectively. At ten minutes, ST was 96 ± 1 versus 97 ± 1 and $T_1$ was 98 ± 1 versus 95 ± 2 per cent, respectively. Train-of-four ratio ($T_4/T_1$) was slightly greater in the divided dose group between five and ten minutes, but this difference was not statistically significant. The maximum difference was found at seven minutes, when it was nine per cent. At five minutes, $T_4/T_1$ was 49 ± 3 per cent with single dose, compared with 57 ± 2 per cent with divided doses (NS) in the arm which was stimulated with TOF continuously. At ten minutes, these values were 64 ± 3 per cent versus 68 ± 3 per cent, respectively (NS). In the arm which received ST, TOF was applied only twice, at five and ten minutes. At five minutes, $T_4/T_1$ was 58 ± 3 per cent with single and 61 ± 3 per cent with divided doses (NS). At ten minutes, these values were 69 ± 5 per cent and 73 ± 4 per cent, respectively (NS).

TABLE Neuromuscular recovery at 0 and 3 min (per cent mean + SEM)

| | *ST* | $T_1$ | $T_4/T_1$ |
|---|---|---|---|
| Single dose | | | |
| 0 min | 11 ± 1 | 7 ± 1 | 0 ± 0 |
| Divided dose | | | |
| 0 min | 9 ± 1 | 7 ± 1 | 0 ± 0 |
| Single dose | | | |
| 3 min | 82 ± 2 | 77 ± 3 | 44 ± 3 |
| Divided dose | | | |
| 3 min | 63 ± 2 | 54 ± 2 | 26 ± 3 |

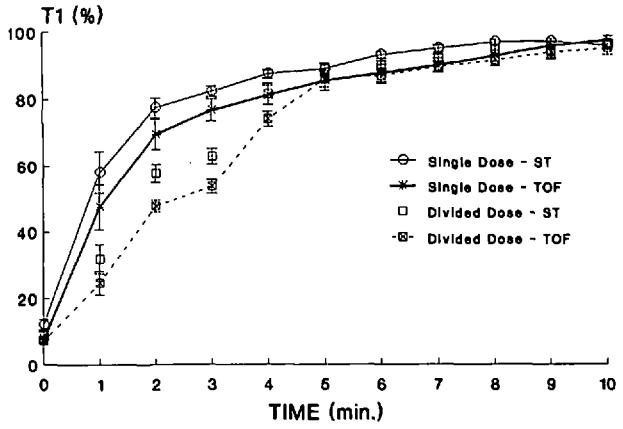


FIGURE 1 First twitch height ($T_1$) and single twitch height (ST) as percentage of control against time after first administration of edrophonium, in patients who received edrophonium as single dose and as divided doses. Error bars represent standard error of the mean (SEM).

## Discussion

This study showed that when edrophonium is used to antagonize atracurium neuromuscular blockade, the recovery observed between five and ten minutes after first administration of edrophonium is not affected significantly by giving divided doses of the drug. Furthermore, after a thiopentone-nitrous oxide-enflurane anaesthetic, train-of-four ratio was often less than 70 per cent, ten minutes after edrophonium administration. The $T_1$ and ST responses were similar, indicating that no major discrepancy exists between ST and TOF during antagonism of blockade with edrophonium.

The total dose of edrophonium used in the study, 1 $mg \cdot kg^{-1}$, was the same as that used by Naguib *et al.*,[2–5] who first described the effectiveness of priming with edrophonium. A priming dose of 0.2 $mg \cdot kg^{-1}$ was reported to be the most effective in the range of 0.05–0.3 $mg \cdot kg^{-1}$.[4] Finally, the three-minute priming interval, when applied to 0.2 $mg \cdot kg^{-1}$ followed by 0.8 $mg \cdot kg^{-1}$, was associated with the shortest reversal time among different combinations tested in another study.[3] The only apparent difference between this study and those of Naguib *et al.*[2–5] is the inhalational agent used; enflurane

was used in this study instead of halothane. Our choice was dictated by the popularity of the agent in clinical practice and in an attempt to "stress the system." Since enflurane impairs recovery,[9,10] it follows that if a less potentiating inhalational anaesthetic had been used, recovery might have been better. This may explain why Naguib *et al.*[2] reported a reversal time, defined as the time from first edrophonium injection to 75 per cent $T_4/T_1$, of 250 sec, or 4.2 min, while most of our patients had not reached 70 per cent $T_4/T_1$ at ten minutes.

The number of patients included in the study was sufficient to detect a clinically significant effect. Power analysis[11] suggests that with the dispersion of values obtained in the study, there was a greater than 80 per cent chance of detecting differences of ten per cent or more. Differences smaller than ten per cent are unlikely to have clinical significance.

One of the hypotheses of this study was that blood flow changes induced by TOF could explain why priming was reported to be effective with edrophonium. If little or no neuromuscular blockade is present, TOF stimulation produces muscle contraction. If applied frequently, these contractions require oxygen, and an increase in muscle blood flow would be expected. This hypothesis was suggested to explain why the measured onset of neuromuscular blockade was shorter if train-of-four stimulation preceded the onset of relaxation.[7] Increased muscle blood flow would increase delivery of the drug to the muscle and thereby accelerate the onset of blockade. A similar hypothesis may be suggested for antagonism of blockade. With neostigmine, such a mechanism may be of little importance. Neostigmine is given during intense neuromuscular blockade, when little muscle contraction is observed. If the priming interval is three minutes, the time course of action of the drug is too slow to produce sufficient recovery of neuromuscular activity to induce large increases in blood flow. Thus, failure of neostigmine priming to accelerate reversal is not surprising. The situation is different with edrophonium. Small doses of the drug (0.2 $mg \cdot kg^{-1}$) produced sufficient recovery of neuromuscular activity to be associated with considerable muscle contraction. For example, in this study, three minutes after the priming dose, $T_1$ was 54 per cent and $T_4/T_1$ was 26 per cent. A second dose given at that time would be likely to reach the TOF stimulated arm preferentially, and the time course of reversal would be accelerated. This phenomenon was not observed in this study. This may have been because the dose response relationship of edrophonium is very flat.[7,12] For example, 0.2 $mg \cdot kg^{-1}$ produced a $T_1$ of 54 per cent after three minutes, whereas 1.0 $mg \cdot kg^{-1}$, i.e., five times as much, produced only 77 per cent. Thus, a small difference in the amount of drug delivered between the two sides would not produce a measurable difference in neuromuscular recovery.

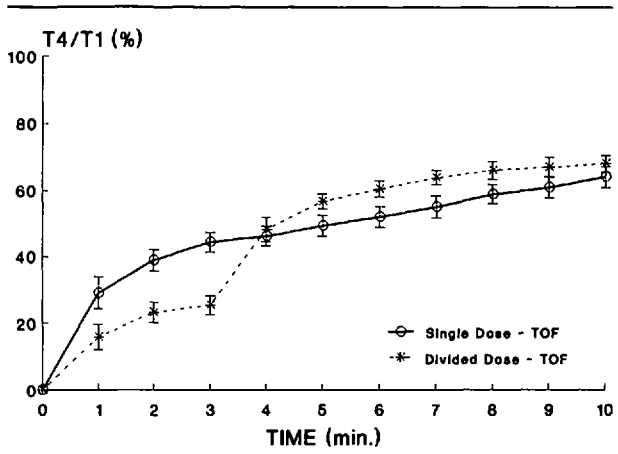


FIGURE 2 Train-of-four ratio ($T_4/T_1$) against time after first administration of edrophonium, for patients who received the drug in single and divided doses. Bars represent standard error of the mean (SEM).

However, there is another possible reason why the priming principle might be effective in certain circumstances. The effectiveness of edrophonium was found to depend critically on the intensity of the block at the time it was administered.[13] The level of blockade in turn depends on the number of relaxant molecules present at the neuromuscular junction. It follows that because of the relatively rapid metabolism of atracurium, the second dose of edrophonium was given when fewer relaxant molecules were present at the neuromuscular junction. Thus, the antagonism would be more effective. Still, the magnitude of this effect might be within the error associated with our measurements, i.e., about ten per cent of either $T_1$ or $T_4/T_1$, and such a small difference would be of little clinical significance.

The time course of edrophonium action also could have been responsible for the failure of this study to reproduce the findings of others. Edrophonium has a rapid onset of action, followed by a plateau phase during which further recovery is slow. Thus, if the effectiveness of the drug is defined as the time to a predetermined effect, such as $T_4/T_1 = 75$ per cent, then a small increase in the effectiveness of the drug could result in a disproportionately important shortening of reversal time. This method of assessment was adopted in the previous studies.[1-5] However, if twitch height or train-of-four ratio is plotted against time, only small differences would be seen, as is the case in the present study. For example, if we had chosen to define reversal time as the interval from first injection of edrophonium to $T_4/T_1 = 60$ per cent, reversal

time would have been nine minutes without and six minutes with priming (Figure 2). However, the actual differences in $T_4/T_1$ between the two groups were small.

It is important to attempt to decrease the time from the injection of a non-depolarizing relaxant until maximum blockade to reduce the time interval between induction of anaesthesia and tracheal intubation. The same concern does not apply to the onset time of neuromuscular relaxant reversal agents because tracheal extubation can be delayed until the patient can demonstrate full return of neuromuscular function. Thus, the techniques which may accelerate the onset of action of reversal agents may not be as crucial to the practice of anaesthesia as those pertaining to the onset of neuromuscular blockade. Considering the low potential yield of the priming technique for edrophonium, and considering its limited usefulness even if it were effective, the administration of edrophonium in divided doses cannot be recommended.

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