# "Priming" with neostigmine: failure to accelerate reversal of single twitch and train-of-four responses

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*Train-of-four stimulation can shorten the apparent onset time of neuromuscular blocking drugs. This study was designed to verify whether the same occurred with neostigmine-assisted recovery, and whether this apparent acceleration could explain the previously reported effectiveness of the priming technique for reversal agents. Fourteen adults received atracurium, 0.5 mg·kg$^{-1}$, during a thiopentone-nitrous oxide-enflurane anaesthetic. The ulnar nerves of both arms were stimulated with train-of-four stimulation every 12 seconds until 1 per cent recovery of first twitch, at which time stimulation in one arm was switched to single twitch. When mean first twitch height reached 10 per cent of control, neostigmine, 0.04 mg·kg$^{-1}$, was administered either as a single bolus, or as a "priming" dose of 0.01 mg·kg$^{-1}$, followed 3 min later by 0.03 mg·kg$^{-1}$. No statistically significant differences were observed between single twitch in one arm and first twitch height of the train-of-four in the other arm for the next 10 min. With priming, first twitch height was 45 ± (SEM) 5 per cent at 5 min and 85 ± 6 per cent at 10 min, compared with 72 ± 5 per cent ($p < 0.05$) and 91 ± 2 per cent (NS) respectively without priming. Train-of-four ratio was 28 ± 3 per cent at 5 min and 65 ± 5 per cent at 10 min with priming, versus 53 ± 4 per cent ($P < 0.05$) and 73 ± 3 per cent (NS) respectively without priming. It is concluded that with neostigmine to reverse atracurium blockade, the response of the first twitch of the train-of-four follows the same time course as single twitch, and priming does not accelerate recovery when reversal is attempted at 90 per cent blockade.*

**Key words**
ANTAGONISTS, NEUROMUSCULAR RELAXANTS: neostigmine; NEUROMUSCULAR RELAXANTS: atracurium; PHARMACODYNAMICS: priming principle; monitoring: train-of-four, single twitch.

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Four studies have suggested that the return to adequate neuromuscular function after administration of atracurium could be accelerated by giving neostigmine or edrophonium[1–4] in divided doses. In these studies, train-of-four stimulation was applied every ten seconds and recovery was defined as a train-of-four ratio greater than 75 per cent.

However, the time course of neuromuscular blockade may be modified by the type of stimulation used.[5] Total neuromuscular blockade appears sooner if train-of-four stimulation is employed instead of single twitch. The difference has been attributed to differences in muscle blood flow induced by the more frequent contractions associated with train-of-four stimulation. Thus, one could hypothesize that a small dose of reversal agent producing a moderate degree of recovery might cause contraction in train-of-four stimulated muscle, which might be associated with increased oxygen requirement and enhanced muscle blood flow. This sequence of events would increase the delivery and effect of a second dose of reversal agent.

The present study was designed to test this hypothesis. The effect of train-of-four stimulation on recovery was assessed by stimulating both ulnar nerves. Train-of-four stimulation was applied to one side and single twitches to the other. The force of contraction of both adductor pollicis muscles was recorded and compared. To measure the effect of priming, the patients were randomized to receive neostigmine either in a single or a divided dose.

## Methods

The protocol was approved by the Hospital Ethics Committee, and informed consent was obtained from the patients. Fourteen adult subjects, ASA physical status I or II, and scheduled for elective surgery, were included in the study. Patients with hepatic, renal, or neuromuscular disease were excluded, as were those with electrolyte abnormality and those taking any medication known or suspected of interfering with neuromuscular function.

Premedication with atropine, 0.006–0.01 mg·kg$^{-1}$, or

glycopyrrolate, 0.003–0.005 mg·kg$^{-1}$, and morphine, 0.1 mg·kg$^{-1}$, or meperidine, 1.0 mg·kg$^{-1}$, was given intramuscularly 1 h before the scheduled start of the surgical procedure. On arrival in the operating room, the patients' ECG was monitored continuously. To minimize interference with neuromuscular recording in both arms, arterial blood pressure was measured with a non-invasive device (DINAMAP) attached to the leg. Anaesthesia was induced with thiopentone, 3–5 mg·kg$^{-1}$, and maintained with nitrous oxide (70 per cent) and enflurane in oxygen. The end-tidal concentration of enflurane was maintained constant in each patient, and ranged from 0.5 to 1 per cent, as measured by a mass spectrometer (SARA). Ventilation was controlled to maintain end-tidal carbon dioxide partial pressure at 30–35 mmHg.

Both hands and forearms were immobilized in a splint, and the force of contraction of both adductor pollicis muscles was measured with a Grass FT10 transducer. The ulnar nerves were stimulated supramaximally at the elbow with square pulses of 0.2 ms in duration, at a frequency of 2 Hz for 2 s. This train-of-four pattern was repeated every 12 s. After a stable baseline had been obtained, atracurium, 0.5 mg·kg$^{-1}$, was injected rapidly, and tracheal intubation was performed when maximum twitch depression was attained.

When first twitch height had recovered to one per cent, i.e., when a twitch was barely perceptible in either arm, one side was allocated at random to receive single twitch stimulation every 12 s, whilst train-of-four stimulation continued to be applied to the other side every 12 s. When the mean value of first twitch height relative to control measured in one arm and single twitch height relative to control measured in the other arm reached ten per cent, the patients were randomized to receive neostigmine 0.04 mg·kg$^{-1}$ either in one single dose, or as a priming dose of 0.01 mg·kg$^{-1}$, followed by 0.03 mg·kg$^{-1}$ 3 min later. Neuromuscular monitoring continued for at least 10 min after the administration of the first or single dose of the reversal agent. Train-of-four stimulation was applied once at 5 min and once again at 10 min on the arm that otherwise received single twitch stimulation.

At each minute after the first injection of the reversal drug, first twitch height, expressed as a percentage of its control value, was compared with the value of single twitch height, expressed as a percentage of its own control, in the contralateral arm of the same patient. At 5 and 10 min, train-of-four ratios obtained in both arms were compared. Paired Student's t test was used for this purpose. The effect of administering neostigmine in divided doses versus single dose was assessed by comparing first twitch height and train-of-four ratio every minute after injection of the first or only bolus dose. Unpaired Student's t test was utilized for these comparisons.

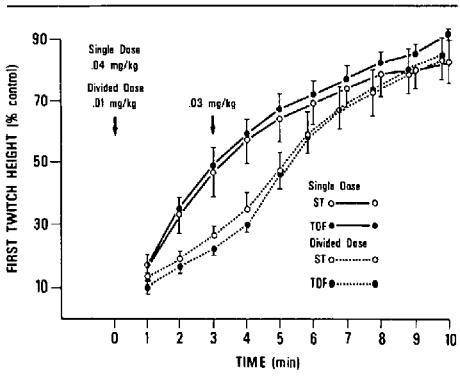


FIGURE 1 Twitch height of the first response in the train-of-four (TOF) and of the response to single twitch stimulation (ST), with neostigmine given as a single dose (solid lines) or in divided doses (dashed lines), versus time after administration of the first or single dose of neostigmine. The TOF responses of single and divided doses are statistically different from each other ($p < 0.05$) between 2 and 6 min.

Results are presented as mean values ± standard error of the mean (SEM). A p value of 0.05 or less was considered to indicate statistical significance.

## Results

There were five males and nine females in the study. Mean age was (± SEM) 47 ± 4 years and mean weight was 69 ± 3 kg. There were no significant differences in the demographic data of the patients who received neostigmine as a bolus compared with those who were given a priming dose.

Neostigmine was first administered 46.3 ± 2.0 min after injection of atracurium. At this time, the difference between the response in the two arms was 2.4 ± 1.6 per cent. First twitch height was 10.8 ± 1.0 per cent of control in the arm which received train-of-four stimulation, and single twitch height was 9.9 ± 1.2 per cent of control in the arm which was stimulated with single twitches.

First twitch height was very similar to single twitch height at all times after injection of neostigmine in patients who received the drug in single or divided doses (Figure 1). The mean difference between the two values was 2.5 per cent, with a range of 0 to 8 per cent. The train-of-four ratios at 5 min and 10 min were also very similar, and independent of the mode of stimulation.

Both first twitch and train-of-four recovery were initially slower if neostigmine was given in divided doses (Figures 1 and 2). Between 2 and 6 min after the first injection of neostigmine, the first twitch in the train-of-

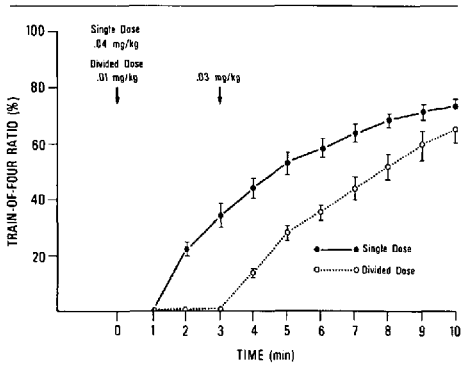


FIGURE 2 Train-of-four ratio with neostigmine administered as a single dose (solid lines) or in divided doses (dashed lines) versus time after administration of the first or single dose of neostigmine. The responses are statistically different from each other between 2 and 9 min.

four was significantly greater ($p < 0.05$) in patients who received the reversal agent as a single bolus. After 7 min, the effect of neostigmine given in divided doses approached, but never exceeded that of single doses. Train-of-four ratio was less in the group which received a priming dose, and the difference was statistically significant ($p < 0.05$) in the range 2–9 min (Figure 2).

The priming technique did not appear to offer any advantage even if time was measured after the administration of the second dose. For example, first twitch height and train-of-four ratio were 76 ± 5 per cent and 64 ± 3 per cent respectively, 7 min after administration of neostigmine as a single dose. These values were 85 ± 6 per cent and 65 ± 5 per cent respectively (NS), 7 min after the administration of the second dose of neostigmine in patients who received a priming dose of the drug.

**Discussion**

The results of this study suggest that giving neostigmine in divided doses three minutes apart does not offer any advantage when compared with the same quantity of drug given as a single dose. In fact, the rate of recovery was significantly slower in the first 6 min after the first injection of reversal agent in patients who received divided doses. These results also indicate that train-of-four stimulation applied every 12 seconds is a useful pattern for the study of the time course and effect of neostigmine. With train-of-four stimulation, first twitch height is equivalent to single twitch height and train-of-four ratio data are also obtained.

Taking into consideration the dispersion of values found in this study, power analysis[6] indicates that the number of patients in this study was sufficient to detect differences of 10–12 per cent or less in either twitch height or train-of-four ratio between single and divided dose groups. Thus, it is highly unlikely that a clinically significant effect of priming was missed. A train-of-four value of about 70 per cent, which corresponds to recovery of adequate respiratory function,[7] was not reached for 10 min after injection of neostigmine, with or without priming. When comparing first twitch of the train-of-four and single twitch height, the number of patients was sufficient to detect differences as small as five to six per cent. Such small differences are not clinically significant. Thus, it is expected that in studies which have examined the time course or potency of neostigmine with train-of-four stimulation every 12 seconds or less frequently,[8–14] the first response of the train-of-four could be regarded as equivalent to the response to single twitch stimulation.

In this study, time zero was defined as the time of administration of either the single dose or the priming dose. This definition is consistent with that employed in the studies which first described the use of the priming technique for reversal agents.[1–4] However, it is different from that commonly used when studying priming for the non-depolarizing neuromuscular blockers. In this case, time is counted from the administration of the second dose.[15,16] If this more commonly used definition was used in the case of reversal agents, the priming technique would appear more effective by shifting the priming curves (Figures 1 and 2) 3 min to the left, with no change in the single dose curves. Even with this data manipulation, the effect of priming is not significantly different from that of a single dose.

During onset of neuromuscular blockade, train-of-four and single twitch responses may differ markedly.[5] A probable explanation for this observation is muscle contraction-induced changes in blood flow. In the absence of neuromuscular blockade, train-of-four stimulation produces four times as many contractions as single twitch stimulation. Thus, muscle oxygen requirement is likely to be greater. It follows that blood flow is probably also greater, to keep up with metabolic demand. As a result, the administration of a neuromuscular blocking agent is expected to produce preferential delivery of the drug to the muscle stimulated with the train-of-four pattern, and onset time will be shorter. Assuming this preferential delivery of a drug to contracting muscle, such an effect is unlikely to occur when neuromuscular blockade is profound, because the size of contraction and presumably oxygen requirement of muscle are both very small. This situation prevails when reversal is attempted. Even 3 min after a priming dose of neostigmine, mean

first twitch height increased to only 25 per cent and fourth twitch was barely perceptible. Presumably, this would correspond to only a small increase in oxygen requirement and muscle blood flow. It follows that the second dose would not be distributed preferentially to the side to which train-of-four stimulation is applied. Thus, contraction-induced adjustments in blood flow are a likely explanation for the shorter onset of neuromuscular blockade observed with train-of-four stimulation, and the absence of such an effect with neostigmine.

The differences in methodology between this study, which demonstrated no acceleration of reversal with neostigmine priming, and a previous report[1] which did, are very minor and unlikely to explain the different results. The dose of atracurium, $0.5\,mg \cdot kg^{-1}$, was indentical in both studies. The inhalational agent used here was enflurane, versus halothane in the previous report. Total neostigmine dose was $0.04\,mg \cdot kg^{-1}$, versus $0.05\,mg \cdot kg^{-1}$ previously. The combined effect of the different inhalational anaesthetic and the lower dose of neostigmine in this study probably explains why a train-of-four ratio of 75 per cent was not attained at 10 min compared with 7 min in the other report.[1] However, these methodological differences are unlikely to explain why priming was effective in one study and not in the other. The interval between successive trains was 12 seconds in the present study, compared with ten seconds in Abdulatif *et al.*'s study.[1]

However, the end-point chosen might be of some importance. We chose to plot first twitch height and train-of-four ratio as a function of time. Abdulatif *et al.*[1] measured the time to an arbitrarily defined end-point (train-of-four ratio of 75 per cent). The last method might lead to an exaggeration of the differences because the train-of-four ratio changes very slowly with time, after the first few minutes. For example, examination of Figure 2 indicates that with a single dose of neostigmine, little recovery took place from 7 to 10 min. Thus, a patient may take a relatively short time to achieve a train-of-four ratio of 65 per cent or 70 per cent, but much longer to reach 75 per cent. The use of the priming technique may conceivably shorten the time to reach 75 per cent considerably without improving train-of-four ratio by more than five or ten per cent. Therefore, it is suggested that the time to an arbitrarily defined end-point may be altered considerably without any clinically significant change in first twitch height or train-of-four ratio.

The clinical use of a priming dose of neostigmine might theoretically be justified in a limited number of cases. One might argue that a priming dose might displace relaxant molecules away from the receptor, thus making the second dose more efficacious. However, it appears that giving neostigmine in divided doses does not have any advantage over a single dose of the drug, at least when given to antagonize atracurium blockade.

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## Résumé

*La stimulation en train-de-quatre peut raccourcir le délai mesuré d'action des curares. Cette étude avait pour but de vérifier si ce phénomène se produisait lors de la neutralisation du bloc par la néostigmine, et si ceci pouvait expliquer l'efficacité déjà décrite de la technique de l'amorce pour les anticholinestérasiques. On a donné 0.5 mg · kg$^{-1}$ d'atracurium à 14 adultes au cours d'une anesthésie au thiopental, protoxyde d'azote et enflurane. On a stimulé le nerf cubital de chaque bras en utilisant le train-de-quatre toutes les 12 secondes, jusqu'à ce que la réponse au premier twitch récupère à un pour cent. Alors, on a changé le mode de stimulation de l'un des bras pour appliquer une stimulation unique toutes les 12 secondes. Lorsque la moyenne de la réponse mesurée dans les deux extrémités atteignait dix pour cent, on administrait de la néostigmine, soit en une seule dose de 0.04 mg · kg$^{-1}$, soit en une dose d'amorce de 0.01 mg · kg$^{-1}$, suivie trois minutes plus tard de 0.03 mg · kg$^{-1}$. Pendant les dix minutes suivantes, on n'a pas noté de différences significatives entre le twitch unique enregistré dans un bras et le premier twitch du train-de-quatre dans l'autre bras. Avec la dose d'amorce, le premier twitch était de 45 ± (ETM) 5 pour cent après cinq minutes et 85 ± 6 pour cent après dix minutes. Après une dose unique, ces valeurs étaient de 75 ± 5 pour cent ($p < 0.05$) et de 91 ± 2 pour cent (N.S.), respectivement. Avec l'amorce, le rapport du quatrième au premier twitch était de 28 ± 3 pour cent après cinq minutes et de 65 ± 5 pour cent après dix minutes. Sans amorce, ce rapport s'établissait à 53 ± 4 pour cent ($p < 0.05$) et 73 ± 3 pour cent (N.S.), respectivement. On en conclut que lorsque la néostigmine est utilisée pour neutraliser le bloc neuromusculaire produit par l'atracurium, la réponse du premier twitch du train-de-quatre est semblable à celle du twitch unique. De plus, le principe de l'amorce appliqué à la néostigmine n'accélère pas la récupération, lorsqu'on donne cet anticholinestérasique pour neutraliser un bloc de 90 pour cent.*