Optimum time for neostigmine reversal of atracurium-induced neuromuscular blockade

Hans Kirkegaard-Nielsen MD,
Hans Søren Helbo-Hansen MD, Peter Lindholm MD,
Inge Krogh Severinsen MD,
Henrik Stougaard Pedersen MD, Erik Weber Jensen MSc

Purpose: The aim of the study was to determine the optimum time for administration of neostigmine during recovery from atracurium-induced neuromuscular blockade.

Methods: The study comprised 103 patients anaesthetised with midazolam, fentanyl, thiopentone, halothane, and nitrous oxide. Relaxation was induced with atracurium $0.5 \text{ mg} \cdot \text{kg}^{-1}$ and maintained with supplements of $0.15 \text{ mg} \cdot \text{kg}^{-1}$. The ulnar nerve was stimulated with train-of-four (TOF) and double burst stimulation (DBS). Evoked MMG responses were recorded. Patients were randomized to spontaneous recovery ($n = 20$) or to assisted recovery by neostigmine ($0.07 \text{ mg} \cdot \text{kg}^{-1}$) at varying intervals (6–50 min) from the last atracurium dose ($n = 83$).

Results: The reversal time (time from administration of neostigmine to TOF ratio 0.7) was always <13 min, when T_1 (first twitch in TOF) was detectable or when D_1 (first twitch in DBS) was $>5\%$. Total assisted recovery time (time from last supplemental atracurium dose to TOF ratio 0.7) increased with increasing T_1 and D_1 twitch heights ($P < 0.05$). The curve fitted to the scattergram with total assisted recovery time vs time from last atracurium supplement to neostigmine administration decreased to reach a minimum after which it increased to approach the line of identity. The minimum of the curve (total assisted recovery time 30.7 min) was reached when neostigmine was given 18.6 min after last atracurium supplement. At this time the T_1 and D_1 twitch height averaged 4 and

8% respectively. If prolongation of the minimum total recovery time of 2.5% is accepted, neostigmine can be given at T_1 and D_1 twitch height values of 0 to 8% and 4 to 15%, respectively.

Conclusion: The optimum time for neostigmine administration, taking both the reversal time and total recovery time into consideration, is when $0 < T_1 < 8\%$ or when $5 < D_1 < 15\%$. Giving neostigmine at more profound degrees of blockade prolongs reversal time, while giving neostigmine later in the recovery phase prolongs total recovery time.

Objectif: Déterminer le moment idéal pour l'administration de la néostigmine pendant la phase de récupération du bloc neuromusculaire induit par l'atracurium.

Méthodes: Cette étude évaluait 103 patients anesthésiés au midazolam, fentanyl, thiopentone, halothane et protoxyde d'azote. La relaxation était induite par l'atracurium ($0,5 \text{ mg} \cdot \text{kg}^{-1}$) et entretenue avec des suppléments de $0,15 \text{ mg} \cdot \text{kg}^{-1}$. Le nerf cubital était stimulé avec le train-de-quatre (TOF) et la suppression du double burst (DBS). Les réponses MMG évoquées étaient enregistrées. Les patients étaient répartis au hasard entre récupération spontanée ($n = 20$) et assistée par la néostigmine ($0,07 \text{ mg} \cdot \text{kg}^{-1}$) à intervalles variés (6–50 min) après la dernière doses d'atracurium ($n = 83$).

Résultats: Le temps de neutralisation (l'intervalle entre l'administration de la néostigmine et le retour du rapport TOF 0,7) était toujours <13 min, au moment où T_1 (premier twitch du TOF) était détecté ou quand D_1 (premier twitch du DBS) était $>5\%$. Le temps de la récupération assistée (l'intervalle entre la dernière dose supplémentaire d'atracurium et le rapport TOF = 0,7) augmentait simultanément avec l'ampleur de T_1 et D_1 ($P < 0,05$). La courbe du diagramme de dispersion ajustée à la récupération totale assistée vs l'intervalle entre le dernier supplément d'atracurium et l'administration de la néostigmine diminuait pour atteindre un minimum après quoi elle augmentait pour s'approcher de la ligne d'identité. Le creux de la courbe (temps total de récupération assistée 30,7 min) était atteint quand la néostigmine était administrée 18,6 min après le dernier supplément d'atracurium. À ce moment, la hauteur des twitch T_1 et D_1 était respectivement de 4 et 8%.

Key words

ANTAGONISTS: neostigmine;

MONITORING: neuromuscular transmission, train-of-four, double burst stimulation;

NEUROMUSCULAR RELAXANTS: atracurium.

From the Department of Anaesthesia and Intensive Care, Odense University Hospital, DK-5000 Odense C, Denmark.

Address correspondence to: Dr. H. Kirkegaard-Nielsen, Department of Anaesthesia and Intensive Care, Odense University Hospital, DK-5000 Odense C, Denmark.

Fax +45 66132854.

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Conclusion: En considérant à la fois le temps de neutralisation et le temps total de récupération, le moment idéal pour administrer la néostigmine se situe quand $0 < T_1 < 0,8\%$ ou quand $5 < D_1 < 15\%$. L'administration de la néostigmine à des niveaux de bloc plus profonds prolonge le temps de neutralisation; l'administration plus tardive de néostigmine pendant la période de récupération prolonge le temps de récupération totale.

The time from administration of neostigmine during recovery from non-depolarizing neuromuscular blockade until the train-of-four (TOF) ratio recovers to 0.7 (reversal time) depends upon the degree of blockade at the time of reversal.¹⁻⁵ Moderate and shallow degrees of atracurium-induced blockade are promptly and completely reversed by neostigmine.^{2,6-9} Reversal from profound degrees of atracurium induced blockade (no response to TOF stimulation) has also been studied.^{4,10,11} Neostigmine administered during profound blockade reduces the time from administration of the last supplementary dose of atracurium until the TOF ratio has recovered to 0.7 (total recovery time), but the reversal time is long and very variable and no time is saved compared with that after reversal at 10% recovery of the first twitch in TOF (T_1). Therefore, reversal of profound blockade has no clinical advantage.

The above studies dealt only with reversal from isolated narrow ranges of different degrees of neuromuscular blockade and, furthermore, focused mainly on the reversal time. Thus, the borderline between prompt and complete reversal, and slow and unpredictable reversal is uncertain. The aim of the present study was to determine the optimum time for administration of neostigmine during recovery from atracurium-induced neuromuscular blockade.

Methods

Patients

We studied 103 ASA physical status I-II adult patients (18 to 60 yr) undergoing elective gynaecological surgery. Patients with a body weight >80 kg, suffering from neuromuscular disease, or under treatment with drugs, which might interfere with neuromuscular transmission, were excluded. The protocol was approved by the local Ethics Committee, and written informed consent was obtained.

Anaesthesia

The patients received premedication with dixyrazine (a phenothiazine derivative) 50 mg *po* the night before surgery. Anaesthesia was induced with midazolam 0.04

mg $\cdot$ kg⁻¹ and fentanyl 3 μ g $\cdot$ kg⁻¹ followed by thiopentone 5 mg $\cdot$ kg⁻¹ and maintained with halothane 0.5% end-tidal concentration (Normac®, Datex, Finland), 65 to 70% nitrous oxide in oxygen, and supplementary doses of 100 μ g fentanyl, 50 mg thiopentone or 1 mg midazolam as required, according to heart rate and blood pressure. Ventilation was adjusted to maintain the end-tidal carbon dioxide partial pressure between 4.9–5.7 kPa (37–43 mmHg) (Normocap®, Datex, Finland). Temperatures were monitored continuously in the nasopharynx or oesophagus and at the hand used for the neuromuscular monitoring. (TR9®, Ellab, Denmark). The patient was covered with warm blankets, the saline used for infusion was warmed, and the temperature in the operation theatre was kept $>20^\circ\text{C}$.

Neuromuscular blockade

Neuromuscular blockade was induced with a bolus dose 0.5 mg $\cdot$ kg⁻¹ of atracurium and maintained with supplementary doses of 0.15 mg $\cdot$ kg⁻¹ atracurium whenever the height of the first twitch of the TOF (T_1) recovered to 15% of the control twitch height ($T_{1\text{control}}$).

The patients were allocated randomly either to spontaneous recovery ($n = 20$) or to assisted recovery by 0.07 mg $\cdot$ kg⁻¹ neostigmine (equivalent to 5 mg $\cdot$ kg⁻¹) and 0.028 mg $\cdot$ kg⁻¹ atropine (equivalent to 2 mg $\cdot$ 70 kg⁻¹) ($n = 83$). The patients allocated to neostigmine assisted recovery were further allocated randomly to receive neostigmine at varying time intervals (6–50 min) from the last supplementary dose of atracurium.

Neuromuscular monitoring

The ulnar nerve was stimulated supramaximally at the wrist using 0.2 or 0.3 msec square wave currents (Myotest DBS®, Biometer, Denmark). Currents of 0.3 msec were used if currents of 0.2 msec did not secure supramaximal stimulation. Initially single twitch (1 Hz) stimulation was used. When the response after approximately 10 min was stable, the stimulation mode was switched to train-of-four stimulation (TOF: four stimuli at 2 Hz delivered every 12 sec), and the height of the first twitch in TOF (T_1) recorded as the control twitch height ($T_{1\text{control}}$). When response to TOF disappeared after administration of atracurium the stimulation mode was switched to double burst stimulation (DBS: burst of three stimuli at 50 Hz followed 0.75 sec later by an identical burst) delivered every 20 sec. Intubation was performed, when response to DBS disappeared.

Patients allowed to recover spontaneously received repeated sequences of four DBS and six TOF stimulation patterns from administration of the last supplementary dose of atracurium. Only responses to the fourth DBS stimulation and to the sixth TOF stimulation in

the DBS and TOF sequences, respectively, were recorded.

Patients allocated to neostigmine assisted recovery received DBS stimulation from administration of the last supplementary dose of atracurium. The stimulation mode was switched to TOF at reappearance of response to DBS stimulation. Four DBS stimulations were later interposed 80 sec before the appointed time of administration of neostigmine (time of reversal). Only responses to the fourth DBS stimulation were recorded. The TOF response at the time of reversal was obtained by linear extrapolation of the TOF responses preceding the four DBS stimulations.

Evoked contractions of the adductor pollicis muscle were measured using a force-displacement transducer with a pre-load of 300 g (Myograph 2000, Biometer, Denmark). The T_1 and the twitch heights of the first and second twitch in DBS (D_1 and D_2 , respectively) were measured as % of T_1 control. The twitch heights were recorded from the digital display on the Myograph. Due to filtering in the analogue-to-digital converter in the Myograph, twitch heights <4% did not consistently appear on the digital display. Therefore, twitch heights <4% identified on the graph but not appearing on the digital display were given the value 2%. Neuromuscular monitoring continued until the TOF ratio recovered to >0.7.

Definitions

Reversal time: Time from administration of neostigmine until the TOF ratio recovered to 0.7.

Pre-reversal time: Time from administration of the last supplementary dose of atracurium until administration of neostigmine.

Total spontaneous recovery time: Time from administration of the last supplementary dose of atracurium until the TOF ratio recovered to 0.7 in patients allowed to recover spontaneously.

Total assisted recovery time. Time from administration of the last supplementary dose of atracurium until the TOF ratio recovered to 0.7 in the patients receiving neostigmine (i.e., pre-reversal time plus reversal time).

Statistics

Students t test for unpaired data, least square regression analyses and ANOVA were used, $P < 0.05$ was considered as statistically significant.

Results

The mean $\pm$ SD (range) age and body weight of the patients were 43 ± 7 (24–60) yr and 64.3 ± 7.4 (48–79) kg, respectively.

The time from administration of the initial dose of

FIGURE 1 Time course of D_1 and T_1 twitch heights (%) vs time from administration of the last dose of atracurium in patients allowed to recover spontaneously. Values are mean with standard deviations indicated by horizontal bars. Open circles represent D_1 in percent of T_1 control, open boxes represent T_1 in percent of T_1 control.

atracurium until the TOF ratio recovered to 0.7 was 108 ± 25.7 (58.2–200.7) min. The number of supplementary doses of atracurium ranged from one to four.

The total spontaneous recovery time was 57.1 ± 9.2 (42.8–76.0) (mean $\pm$ SD (range)) min.

The recovery courses of D_1 and T_1 in the group of patients allowed to recover spontaneously are depicted in Figure 1. The times from administration of the last supplemental dose of atracurium until reappearance of D_1 and T_1 and until D_1 and T_1 recovered to 5, 10, 15, 20, 25, 50, 75 and 100%, respectively, are shown. The times from reappearance of D_1 and T_1 and from the times when D_1 and T_1 had recovered to 5, 10, 15, 20, 25, 50, 75 and 100% until the TOF ratio recovered to 0.7 are shown in Tables I and II.

The relationships between T_1 at the time of reversal and total recovery time, and between T_1 and the reversal time are depicted in Figure 2. When T_1 was > zero, the reversal time was <12.7 min. Total recovery time correlated with T_1 ($P < 0.0001$).

The relationships between D_1 at the time of reversal and total recovery time, and between D_1 and the reversal time are depicted in Figure 3. When D_1 was $\leq 5\%$, reversal time was 22.4 ± 6.3 (12.6–41) min, while the total recovery time was 33.8 ± 5.4 (22.6–48) min. When D_1 was >5%, reversal time was <13 min. Total recovery time correlated with D_1 ($P < 0.0001$).

The relationship between time from atracurium supplementation to neostigmine administration (x) and total assisted recovery time (y) is depicted in Figure 4. Correlation analysis revealed a negative correlation

TABLE I Elapsed time from reappearance of D_1 and from when D_1 had recovered to 5, 10, 15, 20, 25, 50, 75 and 100%, respectively, until the TOF ratio reached 0.7 in patients allowed to recover spontaneously. Values are mean $\pm$ SD (range).

D_1 (%)	Elapsed time (min) until TOF ratio 0.7	
Reappearance	46.1 $\pm$ 6.8	(37.1–59.0)
5	41.8 $\pm$ 6.8	(33.8–54.8)
10	38.4 $\pm$ 5.6	(31.8–48.3)
15	35.7 $\pm$ 5.0	(29.8–44.5)
20	33.8 $\pm$ 4.	(27.1–42.3)
25	32.4 $\pm$ 4.6	(25.5–40.6)
50	27.2 $\pm$ 4.0	(21.5–35.0)
75	23.7 $\pm$ 3.7	(18.6–31.6)
100	21.0 $\pm$ 3.6	(16.0–28.8)

Table II Elapsed time from reappearance of T_1 and from when T_1 had recovered to 5, 10, 15, 20, 25, 50, 75 and 100%, respectively, until the TOF ratio reached 0.7 in patients allowed to recover spontaneously. Values are mean $\pm$ SD (range).

T_1 (%)	Elapsed time (min) until TOF ratio 0.7	
Reappearance	39.0 $\pm$ 6.7	(30.8–53.7)
5	35.8 $\pm$ 5.6	(28.1–48.6)
10	32.3 $\pm$ 4.8	(25.1–42.1)
15	30.0 $\pm$ 4.1	(23.7–38.2)
20	27.8 $\pm$ 4.0	(21.8–36.2)
25	26.0 $\pm$ 3.8	(20.5–34.0)
50	19.0 $\pm$ 4.2	(8.2–26.1)
75	13.2 $\pm$ 3.9	(7.2–23.2)
100	4.8 $\pm$ 4.0	(–0.7–10.1)

between pre-reversal time and total assisted recovery time in the interval 6 to 17 min after atracurium supplementation ($P < 0.05$) and a positive correlation between pre-reversal time and total recovery time in the interval 19 to 50 min ($P < 0.0001$). Furthermore, the x-y relationship has a minimum. When two linear regressions were fitted to the data, the least mean square (LMS) was 1720.2. When one linear regression and one exponentially fit was chosen, LMS was 1644.4, which was less than LMS for the double linear function ($P < 0.05$). The complete dependence was modelled by the function $y = -0.32x + 36$ when $x \leq 15$ min, and $y = 57.\exp(-x/12) + x$ when $x > 15$ min. The coefficients were calculated to give the best fit in a LMS sense. The minimum of the curve was at $y = 30.7$ min for $x = 18.6$ min. In other words, the shortest total assisted recovery time of 30.7 min was obtained when neostigmine was administered 18.6 min after the last supplemental dose of atracurium. If the data were grouped by pre-reversal time intervals: Group I pre-reversal time 10 to 16 min, Group II pre-reversal time 16 to 20 min, and Group III pre-reversal time 20 to 31 min, it was found that the mean total

FIGURE 2 The relationship between T_1 at the time of reversal (%) and the total assisted recovery time (min) and between T_1 and the reversal time (min).

recovery time in Group II was smaller than the mean total recovery time in Group I and III respectively ($P = 0.039$). This indicates that the minimum of the curve is in the pre-reversal time interval 16 to 20 min, which is consistent with the finding from the curve, where the analytic minimum can be calculated to 18.6 min.

The shortest total assisted recovery time was shorter than the total spontaneous recovery time ($P < 0.05$). The time gained by assisting recovery averaged 26.3 min.

The temperature at the thenar eminence was $>32.0^\circ\text{C}$ and the central temperature was $>36.0^\circ\text{C}$ at all times.

Discussion

The present study indicates that the optimal time for administration of neostigmine during recovery from atracurium induced blockade is when $0 < T_1 < 8\%$ or when $5 < D_1 < 15\%$. The reversal time increases when neostigmine is administered at more profound degrees of blockade, and the total recovery time increases when neostigmine is given at more shallow degrees of blockade.

End-tidal halothane concentration was kept constant

FIGURE 3 The relationship between D_1 at the time of reversal (%) and the total assisted recovery time (min) and between D_1 and the reversal time (min).

FIGURE 4 The relationship between pre-reversal time (time from atracurium supplementation to neostigmine) and the total assisted recovery time. The relationship was modelled by the functions $y = -0.32x + 36$ for $x \leq 15$ and $y = 57 e^{(-x/12)} + x$ for $x > 15$.

until the TOF ratio had recovered to 0.7. This eliminated sudden movement, which might have interfered with the neuromuscular monitoring. The technique may differ from clinical practice, where the inhalation of halothane often is discontinued at the time of antagonism. As halothane intensifies the effect of neuromuscular relaxants and retards antagonism,^{12,13} the optimum time for

administration of neostigmine, may occur at deeper levels of blockade, if halothane is discontinued earlier, or if it is not used at all.

Both TOF and DBS modes were evaluated as markers, because a previous study indicated that the optimum time for antagonism of vecuronium was at 0–15% recovery of T_1 .¹⁴ Double burst stimulation is capable of monitoring more intense degrees of blockade than TOF¹⁵ and will, therefore, provide a more differentiated measure of the degree of blockade, when T_1 is close to 0%. Both T_1 and D_1 were measured in % of T_1 control. One could argue that D_1 should be measured as % of D_1 control but this would abolish the advantage from the more forceful contractions produced by double burst stimulation. Furthermore it would be bothersome to operate with two different control levels. In the clinical setting, when mechanomyography is used for neuromuscular monitoring, stimulation will be with TOF most of the time and DBS will only be used during deep degrees of blockade.

The design with only one arm used for neuromuscular monitoring posed the problem that TOF and DBS stimulations could not be delivered simultaneously. Furthermore, when switching from TOF to DBS or *vice versa* it took time before the responses to the succeeding stimulation mode had stabilised.¹⁶ These problems were overcome (1) by interposing four DBS stimulations immediately before antagonism, (2) by using the response to the fourth stimulation (representing the stable response coinciding with antagonism), and (3) by linearly extrapolating the responses of the preceding TOF stimulation to the time of antagonism.

Neostigmine was chosen in favour of edrophonium, as neostigmine is more effective than edrophonium in reversal of profound degrees of block.^{2,3,17,18} The dose of neostigmine of $70 \mu\text{g} \cdot \text{kg}^{-1}$ was chosen as we intended to study the maximal antagonising effect. The effect of neostigmine increases with increasing doses to a ceiling, beyond which further amounts of neostigmine produce no additional antagonism.¹⁹ There is, however, no general agreement of the size of the ceiling in humans. Some studies have demonstrated a greater effect of $70\text{--}80 \mu\text{g} \cdot \text{kg}^{-1}$ neostigmine than $40 \mu\text{g} \cdot \text{kg}^{-1}$ neostigmine at reversal from 5–10% T_1 recovery^{5,9,20} while others have demonstrated that the difference between the two doses was negligible.^{21,22} A TOF ratio of 0.70–0.75 is normally considered to reflect adequate recovery from neuromuscular blockade.²³ Thus the neuromuscular monitoring continued until the TOF ratio recovered to >0.70 . However, it has been reported that some muscle weakness may be present even at a TOF ratio of 0.70.²⁴

In order to study reversal from the entire range of dif-

ferent degrees of neuromuscular blockade, we randomised the patients to reversal at different times from the last supplementary dose of atracurium. As we assumed the reversal time to be more variable during profound degrees of blockade, more patients were randomised to reversal at short time intervals (6–10 min) from the last supplementary dose of atracurium than to reversal from more shallow degrees of block (20–40 min).

The reversal time is a function of two processes: (1) spontaneous recovery rate of atracurium and (2) enhanced recovery promoted pharmacologically with neostigmine. The time to peak effect of neostigmine is 8.0 ± 1.9 min (mean $\pm$ SD)²⁰ implying that the maximal effect of neostigmine is achieved within 13 min (mean + 2.576 SD) in approximately 99% of the patients. Further recovery taking place >13 min after antagonism is, therefore, exclusively dependent on the ongoing spontaneous recovery. Based on these data it does not seem reasonable to accept reversal times >13 min.

The results of the present study showed that the reversal time was <13 min in all patients when response to T_1 had reappeared or when D_1 had recovered to >5%. Furthermore, reversal time was >12 min in all patients, when the response to TOF was abolished, or when $D_1 \leq 5\%$. Consequently, reappearance of the response to TOF or recovery of D_1 to 6% may serve as markers for the earliest time for antagonism. A previous study has shown that D_1 reappears before T_1 during recovery.²⁵ Therefore, D_1 may be preferable to T_1 as a predictor as it gives an earlier warning that the optimum time for antagonism is near.

In order to define the optimum point for antagonism, one also has to take into consideration the total recovery time. The total assisted recovery time was found to increase with increasing T_1 and D_1 twitch heights implying a waste of time if neostigmine is given too late. To get a more differentiated picture of the relationship between the degree of block and total recovery time, we also determined the relationship between the total assisted recovery time and the pre-reversal time. This relationship showed that total recovery time initially decreased, reached a minimum, and finally increased again approaching the line of identity. Neostigmine given shortly after atracurium supplementation cannot reverse the blockade totally, and when a TOF ratio of 0.7 finally is reached, neostigmine has lost some of its effect because of the ongoing elimination processes. This is the explanation for the longer total recovery time when neostigmine is given very early in the recovery phase. The curve showed that the minimum total assisted recovery time averaged 30.7 min, when neostigmine was administered 18.6 min after the last supplemental

dose of atracurium. This analytic curve minimum is consistent with the finding that the mean total assisted recovery time in the pre-reversal time interval 16 to 20 min is smaller than the total assisted recovery time in the pre-reversal interval 10 to 16 min and 20 to 31 min respectively ($P < 0.05$). The total assisted recovery time is shorter than the total spontaneous recovery time of 57.0 min ($P < 0.05$). The maximum time gained by giving neostigmine averaged 26.3 min (57.0 minus 30.7 min). In Figure 1 we can see that 18.6 min after the last supplemental dose of atracurium corresponds to a T_1 of approximately 4% and a D_1 of approximately 8%. The fitted curve is flat around its minimum. It is therefore reasonable to accept some variation in the minimum total assisted recovery time. A 2.5% prolongation of the minimum total assisted recovery time implies a pre-reversal time interval from 14.2 to 23.3 min. The pre-reversal time is obtained by solving the equations describing the curve in Figure 4 for a y value of 31.47 min. From Figure 1 it can be seen that this pre-reversal time interval corresponds to a T_1 interval of 0 to 8% and a D_1 interval of 4 to 15%.

The results obtained may be influenced by the anaesthetic technique, the blocking agent and the neostigmine dose. Therefore, one should be cautious about generalising from the results of the present study.

Taking both the reversal time and total recovery time into consideration we conclude that the optimal time for neostigmine administration is when $0 < T_1 < 8\%$ or when $5 < D_1 < 15\%$. Giving neostigmine at more profound degrees of blockade will prolong reversal time and this is clinically undesirable. Giving neostigmine at non shallow degrees of blockade may prolong total recovery time. The D_1 appears superior to T_1 as a marker as D_1 gives an earlier warning of the optimum time for antagonism.

References

- 1 Hennart D, d'Hollander A, Plasman C, De Jonckheere M. Importance of the level of paralysis recovery for a rapid antagonism of atracurium neuromuscular blockade with moderate doses of edrophonium. *Anesthesiology* 1986; 64: 384–7.
- 2 Rupp SM, McChristian JW, Miller RD, Taboada JA, Cronnelly R. Neostigmine and edrophonium antagonism of varying intensity neuromuscular blockade induced by atracurium, pancuronium, or vecuronium. *Anesthesiology* 1986; 64: 711–7.
- 3 Donati F, Lahoud J, McCready D, Bevan DR. Neostigmine, pyridostigmine and edrophonium as antagonists of deep pancuronium blockade. *Can J Anaesth* 1987; 34: 589–93.
- 4 Engbæk J, Østergaard D, Skovgaard LT, Viby-Mogensen

- J. Reversal of intense neuromuscular blockade following infusion of atracurium. *Anesthesiology* 1990; 72: 803–6.
- 5 Beemer GH, Bjorksten AR, Dawson PJ, Dawson RJ, Heenan PJ, Robertson BA. Determinants of the reversal time of competitive neuromuscular block by anticholinesterases. *Br J Anaesth* 1991; 66: 469–75.
- 6 Payne JP, Hughes R. Evaluation of atracurium in anaesthetized man. *Br J Anaesth* 1981; 53: 45–54.
- 7 Basta SJ, Ali HH, Savarese JJ, et al. Clinical pharmacology of atracurium besylate (BW 33A): a new non-depolarizing muscle relaxant. *Anesth Analg* 1982; 61: 723–9.
- 8 Astley BA, Hughes R, Payne JP. Antagonism of atracurium-induced neuromuscular blockade by neostigmine or edrophonium. *Br J Anaesth* 1986; 58: 1290–5.
- 9 Harper NJN, Wallace M, Hall IA. Optimum dose of neostigmine at two levels of atracurium-induced neuromuscular block. *Br J Anaesth* 1994; 72: 82–5.
- 10 Caldwell JE, Robertson EN, Baird WLM. Antagonism of profound neuromuscular blockade induced by vecuronium or atracurium. *Br J Anaesth* 1986; 58: 1285–9.
- 11 Magorian TT, Lynam DP, Caldwell JE, Miller RD. Can early administration of neostigmine, in single or repeated doses, alter the course of neuromuscular recovery from a vecuronium-induced neuromuscular blockade? *Anesthesiology* 1990; 73: 410–4.
- 12 Delisle S, Bevan DR. Impaired neostigmine antagonism of pancuronium during enflurane anaesthesia in man. *Br J Anaesth* 1982; 54: 441–5.
- 13 Baurain MJ, d'Hollander AA, Melot C, Dernovoi BS, Barvais L. Effects of residual concentrations of isoflurane on the reversal of vecuronium-induced neuromuscular blockade. *Anesthesiology* 1991; 74: 474–8.
- 14 Kirkegaard-Nielsen H, May O. Prediction of reversal time and optimal time of neostigmine administration in atracurium blockade. (German) *Anaesthesist* 1994; 43: 528–33.
- 15 Kirkegaard-Nielsen H, May O. Double burst stimulation for monitoring profound neuromuscular blockade: a comparison with posttetanic count and train of four. *Acta Anaesthesiol Belg* 1992; 43: 253–7.
- 16 Kirkegaard-Nielsen H, Helbo-Hansen HS, Lindholm P, Krogh Severinsen I, Bülow K, Jensen EW. Stabilization of the neuromuscular response when switching between different modes of nerve stimulation at surgical degrees of neuromuscular blockade. *J Clin Monit* 1995; 11: 317–23.
- 17 Donati F, Smith CE, Bevan DR. Dose-response relationships for edrophonium and neostigmine as antagonists of moderate and profound atracurium blockade. *Anesth Analg* 1989; 68: 13–9.
- 18 Caldwell JE, Robertson EN, Baird WLM. Antagonism of vecuronium and atracurium: comparison of neostigmine and edrophonium administered at 5% twitch height recovery. *Br J Anaesth* 1987; 59: 478–81.
- 19 Bartkowski RR. Incomplete reversal of pancuronium neuromuscular blockade by neostigmine, pyridostigmine, and edrophonium. *Anesth Analg* 1987; 66: 594–8.
- 20 Kirkegaard-Nielsen H, Helbo-Hansen HS, Lindholm P, Severinsen IK, Bülow K. Time to peak effect of neostigmine at antagonism of atracurium- or vecuronium-induced neuromuscular block. *J Clin Anesth* 1995; 7: 635–9.
- 21 Fox MA, Keens SJ, Utting JE. Neostigmine in the antagonism of the action of atracurium. *Br J Anaesth* 1987; 59: 468–72.
- 22 Jones JE, Hunter JM, Utting JE. Use of neostigmine in the antagonism of residual neuromuscular blockade produced by vecuronium. *Br J Anaesth* 1987; 59: 1454–8.
- 23 Ali HH, Wilson RS, Savarese JJ, Kitz, RJ. The effect of tubocurarine on indirectly elicited train-of-four muscle response and respiratory measurements in humans. *Br J Anaesth* 1975; 47: 570–4.
- 24 Brand JB, Cullen DJ, Wilson NE, Ali HH. Spontaneous recovery from nondepolarizing neuromuscular blockade: correlation between clinical and evoked responses. *Anesth Analg* 1977; 56: 55–8.
- 25 Kirkegaard-Nielsen H, Helbo-Hansen HS, Severinsen IK, Lindholm P, Bülow K. Response to double burst appears before response to train-of-four stimulation during recovery from non-depolarizing neuromuscular blockade. *Acta Anaesthesiol Scand*, in press.