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Antagonism of Low Degrees of Atracurium-induced Neuromuscular Blockade

Dose–Effect Relationship for Neostigmine

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ABSTRACT

Background: Low degrees of residual paralysis (*i.e.*, a train-of-four [TOF] ratio > 0.4) are relatively frequent, difficult to detect, and still potentially harmful. Unfortunately, the appropriate dose of anticholinesterase for this situation has not been determined. This may be of clinical interest because a high dose of neostigmine given at a shallow level of neuromuscular block may produce neuromuscular weakness. The purpose of this study was to investigate the dose–effect relationship of neostigmine to antagonize residual paralysis corresponding to a TOF ratio of 0.4 and 0.6.

Methods: Recovery after 10, 20, 30 μg/kg neostigmine or placebo given at either 0.4 or 0.6 TOF ratio was assessed by acceleromyography in 120 patients undergoing intravenous anesthesia. Time to a 0.9 and 1.0 TOF ratio was measured, and the probability of successful reversal within 10 min after the respective neostigmine doses was calculated. In addition, the dose of neostigmine needed to achieve the recovery targets in 5 or 10 min was also determined.

Results: When given at a TOF ratio of either 0.4 or 0.6, time to 0.9 and 1.0 TOF ratio was significantly shorter with any dose of neostigmine than without. The probability of successful reversal after 20 μg/kg neostigmine was 100% when a TOF ratio of 0.9 was the target; for a TOF ratio of 1.0, the probability was 93% and 67%, dependent on whether the dose of neostigmine was given at TOF ratio of 0.6 or 0.4, respectively. With a dose of 30 μg/kg, a TOF ratio of 1.0 is expected to be reached within approximately 5 min. Low doses of neostigmine are required to reach a TOF ratio of 0.9 or to accept an interval of 10 min.

Conclusion: Reduced doses (10–30 μg/kg) of neostigmine are effective in antagonizing shallow atracurium block. For successful reversal within 10 min, as little as 20 μg/kg neostigmine may be sufficient. These dose recommendations are specific for atracurium and an intravenous anesthetic background.

What We Already Know about This Topic

- Small degrees of residual neuromuscular blockade are difficult to detect and potentially harmful
- Normal doses of neostigmine can produce paradoxical weakness in this situation

What This Article Tells Us That Is New

- In patients with small residual block from atracurium (TOF 0.4–0.6), a small dose of neostigmine (20 μg/kg) produces successful reversal within 10 min

INCOMPLETE neuromuscular recovery may cause reduction in vital capacity and hypoxic ventilatory response, as well as obstruction of the upper airway and disruption of pharyngeal function.[1–5] In addition, Murphy *et al.*[6] recently confirmed that residual paralysis was an important contributing factor to critical postoperative respiratory events. In their case–control study, the mean train-of-four (TOF) ratio when arriving in the postanesthesia care unit was 0.62 in patients experiencing critical respiratory events, whereas it was 0.98 in control patients. Moreover, no control patients had TOF values less than 0.7. Unfortunately, these low degrees of residual paralysis cannot be detected reliably either by the anesthesiologist alone or by using a simple peripheral nerve stimulator. Even with a quantitative nerve stimulator, low degrees of paralysis are difficult to detect, and equipment calibration, continuous monitoring, and recovery to unity are mandatory.[7–9] Moreover, as suggested by Debaene *et al.*,[10] even after a single intubation dose of intermediate-duration relaxant, 45% of the patients arrived in the postanesthetic care unit with a residual neuromuscular block; a large

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majority of them had low degrees of residual paralysis corresponding to a TOF ratio of more than 0.4.

There is now a consensus that these low degrees of residual paralysis are relatively frequent, difficult to detect, and still potentially harmful. However, the appropriate dose of anticholinesterase for this situation has not yet been determined. This may be of clinical interest because several neostigmine side effects are dose dependent, and probably even more importantly in this context, overabundance of acetylcholine at the neuromuscular junction has the potential to increase muscle weakness rather than reverse residual neuromuscular block.[11] Similar results were also reported by others. Indeed, Payne *et al.*[12] observed that 2.5 mg of neostigmine given after neuromuscular recovery may lead to prolonged neuromuscular blockade. *In vitro* data from Bartkowski[13] indicate that high concentrations of anticholinesterase led to randomly appearing hyperactivity with severe fade on stimulation. Goldhill *et al.*[14] confirmed these findings, reporting that a second dose of neostigmine (2.5 mg) given after spontaneous recovery from nondepolarizing block may adversely affect neuromuscular function. Recent findings from Eikermann *et al.*[15] suggest that the upper airway dilator muscles may be especially vulnerable to this paradoxical effect of neostigmine, showing a decrease in inspiratory upper airway volume caused by neostigmine-evoked weakness of upper airway dilator muscles. Moreover, Caldwell[16] reported a decrease in TOF ratio in 8 of 30 patients who received 40 μg/kg of neostigmine 2, 3, or 4 h after a single bolus of 0.1 mg/kg of vecuronium; all these 8 patients had a TOF ratio of more than 0.9 before administration of neostigmine. No such paradoxical effect occurred when neostigmine was given in the presence of residual paralysis or when reduced doses of neostigmine were given (*i.e.*, 20 μg/kg). These data suggest that neostigmine when given in relative excess compared with the degree of neuromuscular blockade may adversely affect neuromuscular recovery by leading to a curare-like effect; the data from Caldwell[16] give convincing evidence that this phenomenon may already occur at current clinical doses of neostigmine. Indeed, it seems that high, but not low, doses of neostigmine given at a shallow level of neuromuscular block may produce neuromuscular weakness. However, the effectiveness of low neostigmine doses in antagonizing shallow block (*i.e.*, TOF ratio 0.4–0.6) has not yet been evaluated when applying the current criteria of adequate neuromuscular recovery. Therefore, this study aimed to investigate the dose–effect relationship of neostigmine to antagonize residual paralysis corresponding to a TOF ratio of 0.4 and 0.6, respectively.

Materials and Methods

The research protocol was approved by the institutional review committee (Centre Hospitalier Universitaire, Nancy, Brabois, France). One hundred twenty adult patients scheduled for elective surgical procedures under general anesthesia (American Society of Anesthesiologists physical status I–III) with tracheal intubation were studied after they gave their written informed consent. Exclusion criteria included neuromuscular, hepatic, or renal disease; abnormal airway anatomy (Mallampati Score 3 and 4); deviation from ideal body weight by more than or equal to 25%; pregnancy; being on medication that influences neuromuscular blockade; or having a history of allergic reaction to drugs used in the study. One hour before arrival in the operating room, patients were premedicated with 1 mg/kg of hydroxyzine orally.

All 120 patients were randomly divided (number draws) into 8 groups of 15 patients: At an acceleromyographic TOF ratio of 0.4, patients in Groups A, B, C, and D received neostigmine (10, 20, 30 μg/kg, or no neostigmine, respectively); at an acceleromyographic TOF ratio of 0.6, patients in Groups E, F, G, and H also received neostigmine (10, 20, 30 μg/kg, or no neostigmine, respectively). Patients in Groups A–C and E–G also received atropine (15 μg/kg). Twitch height (T1) and TOF ratio were documented until complete recovery from neuromuscular block (acceleromyographic TOF ratio, 1.0 ± 0.05).

Induction and Maintenance of Anesthesia

Monitoring, established on arrival in the operating room, included electrocardiography, noninvasive arterial pressure, pulse oximetry, and capnography. Anesthesia was induced in all patients with 2.5–3.5 mg/kg of propofol and 0.2–0.3 μg/kg of sufentanil. Anesthesia was maintained with propofol (8–12 $mg \cdot kg^{-1}\,h^{-1}$), intermittent bolus doses of sufentanil (0.1–0.2 μg/kg), and oxygen–nitrous oxide (50%/50%) until the end of surgery and complete neuromuscular recovery. By using a warming blanket covering the upper body and both arms, the central temperature was maintained over 35°C and peripheral body temperature measured at the thenar eminence of the palm was maintained at least at 32°C. End-tidal partial pressure of carbon dioxide (P_{CO_2}) was maintained between 32 and 36 mmHg.

Neuromuscular Monitoring

Neuromuscular blockade was monitored with acceleromyography (TOF Watch SX®; Schering-Plough, Swords, Co., Dublin, Ireland) as recently recommended for research purposes.[17] The acceleration transducer of acceleromyography was fixed to the volar side of the distal phalanx of the thumb on a small elastic hand adapter applying a constant preload (TOF Watch Handadapter®, Schering-Plough, Swords, Co.). The transducer of acceleromyography was allocated with a random list to the patient's dominant and nondominant hand, and blood pressure cuff and intravenous line were both placed on the arm opposite to the one attached to the acceleromyography transducer. Surface electrodes were placed on the cleaned skin over the ulnar nerve, and the TOF-Watch SX nerve stimulator was used for supramaximal TOF stimulation (four pulses of 0.2 ms in duration, at a frequency of 2 Hz, every 15 s). Acceleromyography was calibrated using the preprogrammed TOF-Watch calibration mode 2. Applying this algorithm, stimulation current was

Table 1. Time in Minutes from Start of Administration of Neostigmine or Placebo to Recovery to a 0.9 and 1.0 TOF Ratio

Prereversal Block	Placebo	Neostigmine Dose Group		
		10 μg/kg	20 μg/kg	30 μg/kg
TOF ratio 0.4				
TOF ratio 0.9				
Median	13*†	6†	6†	4†
Range (minimum to maximum)	7–27	3–12	4–9	3–6
TOF ratio 1.0				
Median	19*	11	9	6
Range (minimum to maximum)	11–30	7–15	6–13	4–11
TOF ratio 0.6				
TOF ratio 0.9				
Median	10*†	4‡	3†	4†
Range (minimum to maximum)	5–16	2–9	2–7	2–6
TOF ratio 1.0				
Median	15*	6	6	5
Range (minimum to maximum)	8–20	4–16	4–14	3–7

Data are median and range.

* $P < 0.0001$ compared with neostigmine, Wilcoxon-Mann–Whitney test. † $P < 0.0001$ compared with 1.0 TOF ratio recovery, paired *t* test. ‡ $P = 0.0004$ compared with 1.0 TOF ratio recovery, paired *t* test.

TOF = train-of-four.

automatically set by the device to 60 mA, and the gain was then automatically adjusted so that the response was set to a 100% value. Then the current was decreased in steps of 5 mA until the response screen value dropped below 90% (*e.g.*, at 35 mA) and then 10% was added to the value before the drop of this value (*e.g.*, 40 mA). The current is then, in this example, set by the device to 40 mA + 10% = 44 mA (supramaximal stimulation). As a last step, the response screen value setting was repeated but now with a stimulus current of 44 mA. After stable base line was obtained with this setting, that is, variation of not more than ±2% of the TOF response for at least 3 min, 0.5 mg/kg of atracurium ($2 \times ED_{95}$ [estimated dose giving 95% twitch depression]) was given as a bolus, and orotracheal intubation was performed. During surgery, bolus doses of atracurium (0.1 mg/kg) were reinjected as clinically needed. Patients in Groups A, B, C, and D received 10, 20, 30 μg/kg of neostigmine, or saline, respectively, once the TOF ratio recovered to 0.4; and patients in Groups E, F, G, and H received 10, 20, 30 μg/kg of neostigmine, or saline, respectively, once the TOF ratio recovered to 0.6. Neuromuscular monitoring was continued until complete recovery of the acceleromyographic TOF ratio (baseline values ±5%).

Recovery Parameters

The recovery data were analyzed as follows.

1. Time course of neuromuscular recovery

- Recovery time: The time interval in minutes after injection of neostigmine (10, 20, 30 μg/kg) or placebo until a TOF ratio recovery to 0.9 and 1.0 was measured. This interval was determined when neostigmine or placebo was given at a TOF ratio of 0.4 and 0.6 (table 1).
- Probability of successful reversal within 10 min after administration of different neostigmine doses and placebo (figs. 1 and 2).

2. Neostigmine requirements to recover from a TOF ratio of 0.4 and 0.6 to a TOF ratio of 0.9 and 1.0: The neostigmine doses to recover to the respective endpoints in 5 and 10 min were calculated (table 2).

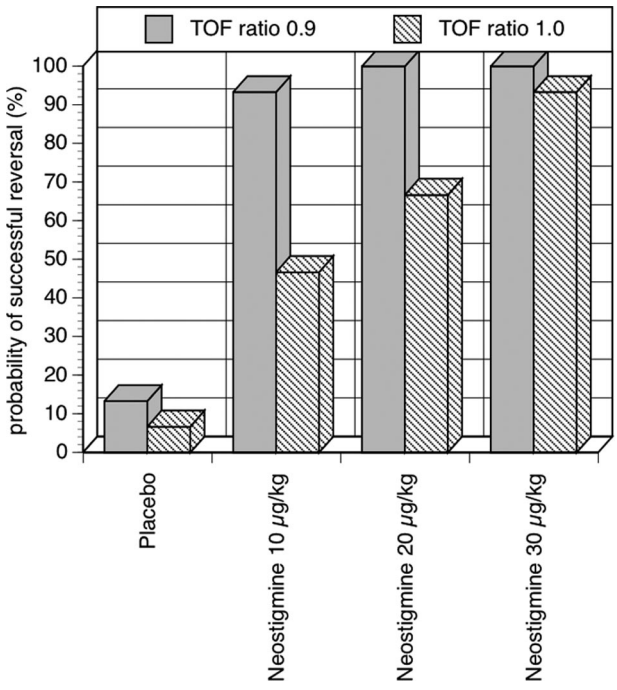

Fig. 1. Probability of successful reversal within 10 min after different doses of neostigmine or placebo. Neostigmine or placebo were given at a train-of-four ratio of 0.4.

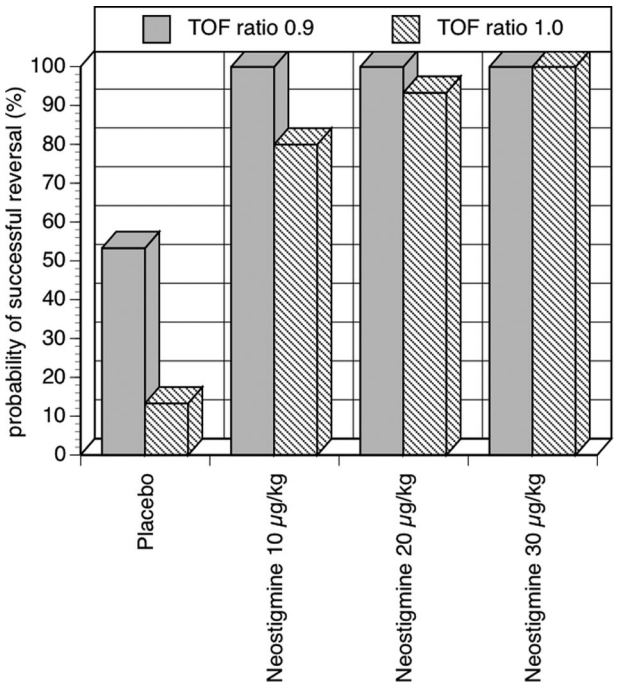

Fig. 2. Probability of successful reversal within 10 min after different doses of neostigmine or placebo. Neostigmine or placebo were given at a train-of-four ratio of 0.6.

Statistical Analysis

The primary efficacy endpoint was the recovery time of 1.0, defined as the time from start of neostigmine or placebo administration until recovery to a 1.0 TOF ratio. The sample size has been estimated using a software program, taking into account the effect size (nQuery Advisor 3.0 Statistical Solutions, Cork, Ireland). Twelve patients were required in each group to detect with 90% power and a 5% α-error (a difference between groups more than or equal to 1.3 SD).

The recovery time of 0.9, defined as the time from start of neostigmine or placebo administration until a 0.9 TOF ratio recovery, was considered as a secondary efficacy endpoint. In addition, the neostigmine dose needed to obtain a 1.0 or 0.9 TOF ratio within 5 or 10 min and the probability of successful reversal within 10 min were also calculated.

Recovery times after the administration of placebo and different neostigmine doses were compared by Wilcoxon-Mann–Whitney test; the dose–effect relationship of the three neostigmine doses was assessed with the Jonckheere-Terpstra test.[18] For each dose of neostigmine or placebo, the respective recovery times of 1.0 and 0.9 were compared with the paired *t* test.

A chi-square test was used to test for differences between groups in proportions of patients successfully reversed within 10 min to 0.9 and 1.0 TOF ratio after neostigmine (10, 20, 30 μg/kg) or placebo administration; this was followed by a Jonckheere-Terpstra test to assess dose–response relationship. The neostigmine dose requirements to obtain a 1.0 or 0.9 TOF ratio within 5 or 10 min, respectively, were calculated as proposed by Smith *et al.*[19] To that end, the TOF ratio was measured once a minute after administration of the placebo or the reversal drug until complete recovery. Thereafter, the respective dose–response relationships were determined at each minute calculating the linear regression of the logit transformation of the TOF response against the logarithm of the dose.[19] Comparison between neostigmine doses were made with Student *t* test. Patient's characteristics and atracurium requirements were compared using the Mann–Whitney U test. A *P* value of less than 0.05 was considered statistically significant.

Results

In this study, no significant differences among the groups with respect to age, weight, height, gender distribution, temperature, and cumulative atracurium dose were found. A TOF ratio of 1.0 ± 5% was obtained in all 120 patients during the recovery phase and no technical failures occurred.

A decrease in TOF ratio did not occur in any patient after the administration of 10, 20, or 30 μg/kg of neostigmine.

Recovery Time

When given at a TOF ratio of either 0.4 or 0.6, time to a 0.9 and 1.0 TOF ratio was significantly shorter with any dose of neostigmine than without; $P < 0.0001$. Increasing the neostigmine dose significantly reduced the time needed to recover from a 0.4 TOF ratio to a 0.9 TOF ratio ($P = 0.002$) or a 1.0 TOF ratio ($P = 0.0001$); no such dose–effect relationship was found when given at a 0.6 TOF ratio (not significant; table 1). For each dose of neostigmine or placebo, recovery to a 1.0 TOF ratio was significantly longer than recovery to a 0.9 TOF ratio (table 1).

Table 2. Dose of Neostigmine Needed to Recover from a TOF Ratio of 0.4 or 0.6 within 5 or 10 min to a TOF Ratio of 0.9 and 1.0, Respectively

	Recovery within 5 min		Recovery within 10 min	
	TOF Ratio 0.9	TOF Ratio 1.0	TOF Ratio 0.9	TOF Ratio 1.0
TOF Ratio 0.4	24 ± 10μg/kg*	34 ± 10μg/kg*†	8 ± 11 μg/kg	25 ± 11μg/kg†
TOF Ratio 0.6	13 ± 12μg/kg*	31 ± 12μg/kg*†	—‡	24 ± 13 μg/kg†

Values are mean (SD).

* $P < 0.001$ compared with the corresponding neostigmine dose at 10 min, Student *t* test. † $P < 0.01$ compared with the corresponding neostigmine dose for a 0.9 TOF ratio recovery, Student *t* test. ‡ Not calculated because the TOF ratio of 0.9 was already reached in < 10 min in most patients in the placebo group and in all patients who received neostigmine (10, 20, or 30 μg/kg).
TOF = train-of-four.

Probability of Successful Reversal

The probability of successful reversal within 10 min after the administration of 10, 20, or 30 μg/kg of neostigmine is displayed in figures 1 and 2.

Neostigmine Requirements

The estimated neostigmine doses needed to reach a 0.9 and 1.0 TOF ratio within 5 and 10 min are shown in table 2. With a dose of 30 μg/kg, a TOF ratio of 1.0 is expected to be reached within approximately 5 min, independent of whether neostigmine was given at a TOF ratio of 0.4 or 0.6. Significantly less neostigmine is required to reach a TOF ratio of 0.9 or if a time interval of 10 min after neostigmine injection is accepted.

Discussion

This study evaluated the ability of reduced doses of neostigmine to facilitate recovery from shallow degrees of residual paralysis (TOF ratio, 0.4–0.6). The most important result is that low doses of neostigmine (10–30 μg/kg) are effective in antagonizing shallow atracurium block. For successful reversal within 10 min, as little as 20 μg/kg of neostigmine may be sufficient. These dose recommendations are specific for atracurium and an intravenous anesthesia/nitrous oxide regimen. They are not valuable when other myorelaxants or volatile anesthetics are used. Indeed, volatile anesthetics potentiate neuromuscular blockade and specifically prolong neostigmine-induced reversal.[20]

To antagonize moderate neuromuscular block corresponding to 1–3 TOF responses, 40–70 μg/kg of neostigmine are required.[21] For shallower—but still potentially harmful—degrees of residual paralysis, no dosing recommendations exist taking into account the current criteria for adequate neuromuscular recovery. Of interest in this context are the findings of Debaene *et al.*,[10] who reported that even 2 h after a single dose of relaxant about 30% of patients still had residual paralysis. However, not one of them had deep or moderate degrees of residual paralysis, but all of them had shallower degrees of residual paralysis. This might raise the question of routine reversal based on one single standard dose of anticholinesterase, which may result in inappropriately high neostigmine doses, in some patients, for the actual degree of residual paralysis and thus, according to the findings of Caldwell,[16] may increase weakness rather than improve neuromuscular recovery. Unfortunately, the neostigmine requirements to reverse these shallower degrees of residual paralysis have not yet been determined, at least not when applying the current criteria for adequate neuromuscular recovery (*i.e.*, a TOF ratio ≥0.9).[22]

One approach to resolve this dilemma of neostigmine dosing when antagonizing lower degrees of residual paralysis might be titration of neostigmine according to the prereversal degree of neuromuscular block, thus linking the dose of neostigmine to the degree of residual neuromuscular block. However, a prerequisite for this concept is the quantification of the prereversal neuromuscular block. Indeed, if the clinician had a method to evaluate residual neuromuscular block, then the dose of neostigmine could be adapted appropriately. Unfortunately, devices that reliably quantify residual neuromuscular blockade are not always available, and if no TOF fade is detected with a simple nerve stimulator, then the TOF ratio is at least 0.4 but it may also be 0.9 or 1.0; a similar case can be made for a TOF ratio of 0.6 when Double-Burst-Stimulation has been used.[7,23,24] However, without residual paralysis, 40 μg/kg of neostigmine but not 20 μg/kg of neostigmine might have paradoxical effects.[16] This has to be considered when the recommendation of a neostigmine dose to reverse shallow neuromuscular block is based on the result of a simple nerve stimulator.

The question to address is what is an appropriate dose of neostigmine for the respective degree of neuromuscular block? In this study, even after the lowest dose of neostigmine, a relevant degree of assisted recovery could be observed and time to complete neuromuscular recovery was significantly reduced. The time to recover from a TOF ratio of 0.4 to 1.0 was reduced from 19 min when spontaneous recovery was allowed to occur to 11 min after 10 μg/kg of neostigmine was given, and increasing the neostigmine dose to 30 μg/kg significantly increased the assisted recovery and further reduced the time interval to 6 min (table 1). When given at a TOF ratio of 0.6, increasing the neostigmine dose from 10 μg/kg to 30 μg/kg did not further accelerate neuromuscular recovery (table 2). This absence of a dose–response relationship may be explained by the rapid recovery still observed after the lowest dose of neostigmine. However, the dose of neostigmine actually needed depends not only on the prereversal degree of neuromuscular block but also on the time interval accepted for complete recovery to occur (table 2). Thus, depending on the clinical context, different doses of neostigmine may be considered.

According to the results of this study at least 20 μg/kg of neostigmine should be given to reverse a TOF ratio of 0.4 or 0.6 within 10 min. Indeed, taking a TOF ratio of 0.9 as the endpoint of adequate neuromuscular recovery, the probability of success was 100% after the administration of 20 μg/kg of neostigmine—whether it was given at a TOF ratio of 0.4 or 0.6. Moreover, 24 of the 30 patients even reached a TOF ratio of 1.0 within the 10-min time interval, and this corresponds to a probability of successful reversal of 66.7 and 99.3% depending whether neostigmine was given at a TOF ratio of 0.4 or 0.6, respectively (fig. 1). In the six remaining patients, the degree of TOF recovery 10 min after the administration of 20 μg/kg of neostigmine was between a TOF ratio of 0.92 and 0.98, and all of them finally recovered to unity within 11 to 14 min after neostigmine was given. Increasing the dose of neostigmine to 30 μg/kg further increased the probability to successful reversal, and now only 1 of 30 patients did not recover to unity within the 10-min interval (fig. 1). In the view of these results, clinically relevant consequences of residual paralysis are unlikely after both doses of neostigmine investigated (*e.g.*, 20 and 30 μg/kg).

Moreover, paradoxical weakness after neostigmine did not occur in any patient in this study. This is not surprising, as only reduced doses of neostigmine (*e.g.*, 10–30 μg/kg) were given, and all patients had shallow degrees of residual paralysis. However, when given in the absence of neuromuscular block, only 20 μg/kg of neostigmine is not associated with the risk of paradoxical weakness[16]; this cannot be ruled out for 30 μg/kg of neostigmine. For these different reasons, 20 μg/kg of neostigmine can be considered an appropriate dose to reverse shallow atracurium neuromuscular blockade within 10 min.

An important finding of this study is the large difference in both the dose of neostigmine and the recovery time irrespective of whether the target was 0.9 or 1.0 TOF ratio. The latter target has been chosen, because it is considered the current benchmark when assessing neuromuscular recovery with acceleromyography. Indeed, as little as 13 μg/kg of neostigmine is sufficient to recover within 5 min from 0.6 to 0.9 TOF ratio, but 31 μg/kg of neostigmine was required when 1.0 TOF ratio was the target (table 2). A similar huge difference was found when focusing on the reversal time (table 2). However, this may have implications.

Indeed, over the past decades, the criteria for adequate recovery from neuromuscular blockade successively increased from a mechanomyographically TOF ratio of 0.7 to 0.9 and even to unity when using acceleromyography,[1–4,8,25,26] but no readjustment of the neostigmine dose occurred. Whether a TOF ratio of 0.7 or significantly higher degrees of neuromuscular recovery were postulated, still 40–70 μg/kg neostigmine given at 1–4 twitch responses after TOF stimulation was proposed. The fixed neostigmine dose may be explained by its ceiling effect.[13] Indeed, once the acetylcholinesterase is completely inhibited, any additional increase in the neostigmine dose will not further improve reversal, and therefore higher neostigmine doses are rather unlikely to be beneficial. However, when the criteria for adequate recovery increase and the dose of neostigmine cannot be adapted accordingly, then waiting for more spontaneous recovery may be the only thing the clinician may do to improve the efficacy of neostigmine-induced reversal. Thus, the question arises whether neostigmine still allows antagonizing moderate degrees of residual paralysis (*i.e.*, 1–3 TOF counts) or whether higher prereversal degrees of neuromuscular block are now required. Indeed, Kirkegaard *et al.* reported of several patients in whom 70 μg/kg of neostigmine given at reappearance of 1–4 TOF responses failed to reverse within 20–30 min to a TOF ratio of at least 0.9.[27] Similar findings were reported by others, as well.[28,29] Thus, first evidence supports the need to wait for more spontaneous recovery to occur before neostigmine-induced reversal can be started. Further research is needed to define the optimal prereversal degree of recovery when residual neuromuscular blockade should be antagonized with neostigmine.

In conclusion, 20 μg/kg of neostigmine may be appropriate to reverse a shallow degree of atracurium residual neuromuscular blockade within 10 min.

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