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NEUROMUSCULAR BLOCKADE (GS MURPHY, SECTION EDITOR)

Neostigmine: Mechanism of Action, Dosing, and Factors Determining Adequacy of Recovery Following Administration

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Abstract

Purpose of Review The endpoint of adequate neuromuscular recovery allowing for safe extubation has been revised several times. A train-of-four (TOF) ratio of at least 0.9 measured at the adductor polices muscle is required to exclude clinically relevant residual paralysis. In particular, upper airway muscle integrity, the hypoxic ventilatory response, and swallowing are still impaired at shallow degrees of residual paralysis. The aim of this review is to evaluate the efficacy of neostigmine in achieving this higher benchmark.

Recent Findings Recent findings suggest that (a) the administration of neostigmine should be delayed until advanced degrees of pre-reversal recovery have occurred (i.e., T1 > 25% or the fourth response to TOF stimulation), or recovery intervals over 15 min have to be accepted; (b) small concentrations of neostigmine (i.e., 20–30 μg/kg) are effective in antagonizing shallow degrees of residual paralysis; and (c) the appropriate administration of neostigmine (i.e., dosing based on monitoring) reduces postoperative complications and improves neuromuscular recovery.

Summary When 40–70 μg/kg neostigmine are administered at the return of 1–4 TOF responses, a recovery interval over 20 min can be expected. Increasing the dose of neostigmine will not further accelerate this interval, but it may increase the risk of paradoxical effects (i.e., the reappearance of fade). A shorter recovery interval is obtained when neostigmine-based reversal is given at more advanced spontaneous pre-reversal neuromuscular recovery.

Keywords Acetylcholinesterase · Anti-cholinesterase · Neostigmine · Residual paralysis · Neuromuscular monitoring · Neuromuscular blockade · Train-of-four

Introduction

In addition to hypnotics and analgesic agents, neuromuscular blocking agents (NMBAs) are frequently used during general anesthesia. They facilitate endotracheal intubation and improve surgical conditions, especially during laparoscopic procedures [1–3]. The introduction of NMBAs in the 1940 by Harold Griffith and Enid Johnson revolutionized anesthesia practice. Neuromuscular blocking agents facilitated the development of cardio-thoracic anesthesia, neuro anesthesia, anesthesia for major abdominal procedures, and critical care [4]. However, in 1954, Beecher and Todd noted that "relaxant anesthesia" was associated with a 35 times higher risk of death [5]. The lack of knowledge related to dosing, monitoring, or reversal of neuromuscular blockade was thought to be at the origin of this significant increase in mortality. In the following decades, devices to monitor neuromuscular block were developed and clinical concepts to avoid residual paralysis were established [6, 7]. Reversal concepts were based on anti-cholinesterase compounds like neostigmine. Neuromuscular monitoring and pharmacological reversal became the key elements of safe management neuromuscular blockade. In the 1970s, the pathophysiological consequences of incomplete neuromuscular recovery were documented. It could be shown that the forced vital capacity (FVC) was reduced by 20–30% at a train-of-four (TOF) ratio of 0.5, and its full recovery

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required higher degrees of recovery of the TOF ratio [8]. Based on these findings, a TOF ratio of 0.7 was suggested as an adequate level of neuromuscular recovery. However, the physiologic effects of residual paralysis were further established over the last decades. Not only are the pulmonary muscles functionally impaired when neuromuscular recovery is incomplete, but hypoxic respiratory control, coordination of the pharyngeal muscles, and integrity of the upper airway are additionally affected. [9–11]. Even at a TOF ratio of 0.8, the risk of pulmonary aspiration due to an impaired ability to swallow and protect the airway is still persistent, and the impaired function of the genioglossus muscle may lead to an inspiratory upper airway obstruction [10, 11]. Thus, even rather small degrees of residual neuromuscular blockade may be potentially harmful to patients and should be prevented.

These findings led to a reconsideration of the definition of adequate neuromuscular recovery. Based on this new information, a TOF ratio > 0.9 is now considered the acceptable threshold indicative of full neuromuscular recovery. However, this increased threshold has consequences for the standard practices of neuromuscular monitoring and reversal. Indeed, a simple peripheral nerve stimulator is unable to detect small but still potentially harmful degrees of residual paralysis, as clinicians are unable to detect fade unless a TOF ratio is below 0.4 [12]. Only objective quantitative monitoring devices may reliably determine whether a TOF ratio of 0.9 has been achieved [13, 14]. In the following section, the efficacy of neostigmine in fully antagonizing neuromuscular blockade (TOF ratio of 0.9 or greater) is reviewed.

Mechanism of Action of Neostigmine

Neostigmine, edrophonium, and pyridostigmine are anticholinesterase drugs used in clinical anesthesia, with neostigmine being most frequently used to accelerate recovery from nondepolarizing neuromuscular blockade. All of these compounds transiently inhibit the activity of the enzyme acetylcholinesterase (AChE), and this inhibition prevents the degradation of acetylcholine. As a consequence of this action, the concentration of acetylcholine rises. At the neuromuscular junction, the increased concentration of acetylcholine competes with the nondepolarizing neuromuscular blocking agent and binds preferentially to the nicotinic acetylcholine receptor on the muscle, thus accelerating the recovery from neuromuscular blockade [6, 15]. This underlying mechanism of action of neostigmine has several clinically relevant consequences:

- Muscarinic side effects: The effect of neostigmine is not limited to the neuromuscular junction, as AChE is present throughout the parasympathetic nervous system in the cardiac, alimentary, and respiratory systems. Therefore, the administration of neostigmine may also result in pronounced bradycardia, increased salivation, bowel motility, nausea, and vomiting, as well as bronchoconstriction. In clinical practice, the cholinergic effects of neostigmine are treated and attenuated by the concomitant administration of either atropine (up to 20 μg/kg) or glycopyrrolate (8–10 μg/kg). Both of these anti-cholinergic drugs block the muscarinic receptors without having any pharmacodynamic effect at the nicotinic acetylcholine receptors at the neuromuscular junction. However, their administration is often associated with tachycardia and arrhythmias.
- Ceiling effect: With increased doses, the effectiveness of anti-cholinesterase drugs reaches a plateau. This plateau is achieved when the enzyme inhibition is almost complete. At this stage, any further increase in the dose will not further increase the effectiveness of the neostigmine [6]. Evidence suggests that for neostigmine, the ceiling effect occurs within the clinical range of the drug, i.e., between 40 and 70 μg/kg [6].
- Minimum degree of spontaneous recovery: Neostigmine is not effective as a reversal agent if neuromuscular blockade is profound; some degree of spontaneous recovery is required before reversal is attempted. Moreover, increasing the threshold of acceptable neuromuscular recovery (from a TOF ratio of 0.7 to a TOF ration of 0.9) has resulted in a reconsideration of degree of spontaneous recovery that is required at the time of reversal [16].

Therapeutic Range of Neostigmine

Depth of nondepolarizing neuromuscular block is determined by the balance between the concentrations of neuromuscular blocking agent (NMBA) and acetylcholine at the neuromuscular junction, and recovery depends on increasing acetylcholine concentration relative to the NMBA. Neostigmine increases the concentration of acetylcholine by inhibiting its degradation and thus facilitates neuromuscular recovery. However, as the concentration of acetylcholine is limited by the amount released, the effectiveness of neostigmine reaches a plateau with increasing doses. The apparent efficacy of neostigmine to treat residual paralysis depends primarily on three variables: the selected endpoint of neuromuscular recovery, the dose of neostigmine given, and the level of spontaneous recovery when neostigmine reversal is initiated [6].

- Selected threshold of neuromuscular recovery: Increasing the threshold of safe neuromuscular recovery to a TOF ratio of at least 0.9 may impact the ability of neostigmine to achieve full neuromuscular reversal. Kirkegaard et al. reported that increasing the endpoint for safe neuromuscular recovery from a TOF ratio of 0.7 to a TOF ratio of 0.9 resulted in significantly fewer patients meeting criteria

for safe tracheal extubation [17]. In this investigation, the authors assessed the effectiveness of neostigmine-based reversal of cisatracurium neuromuscular blockade. They determined that when 70 μg/kg neostigmine was given in the presence of two TOF responses, it took 7.6 min (range 3.2–14.1) to reach a TOF ratio of 0.7. However, this interval increased to 9.8 min (range 5.5–25.0) when the threshold was increased to a TOF ratio of 0.8, and to 20.2 min (range 6.5–70.5) when the threshold was increased to a TOF ratio of 0.9. Several other authors have confirmed these findings [18, 19]. Thus, at a TOF ratio of 0.7, the peak effect of neostigmine occurred within 10 min, with the new benchmark (TOF ratio of 0.9); its peak effect is delayed to 20 min. However, intervals over 15 min are probably poorly accepted in clinical practice and may result in increased operating room times.

- Dose of neostigmine: There is evidence in the literature demonstrating that increasing the dose of neostigmine cannot further accelerate neuromuscular recovery. Kirkegaard-Nielsen et al. compared the recovery patterns from atracurium-induced neuromuscular blockade after 35 and 70 μg/kg neostigmine [20]. While the larger dose led to a faster times to the maximum effect, the maximum T1 response was almost identical in both groups (78 and 79%, respectively), with the TOF ratio being similar (43 vs 51%, respectively). Similar results have been reported by other investigators. This limitation may be explained by the ceiling effect of neostigmine. Moreover, any further increase of the dose of neostigmine may lead to the reappearance of fade. This paradoxical effect of neostigmine appears to be inconsistent with the current conception of neostigmine-based reversal. However, neostigmine can lead to paradoxical neuromuscular effects, especially in patients receiving little or no neuromuscular blocking agents. Neostigmine 2.5 mg/kg restored twitch tension and abolished tetanic fade, but a second dose of 2.5 mg neostigmine produced twitch depression and tetanic fade [21]. In patients not given neuromuscular blocking agents, tetanic fade could be seen in some subjects after 2.5 mg neostigmine, and for others, 5.0 mg was needed to achieve this same result. Goldhill et al. [22] reported a small accentuation of TOF fade with a second, but not a first, 2.5 mg dose of neostigmine given to reverse shallow neuromuscular blockade when the TOF ratio was 0.5. These effects were more marked if reversal was attempted at a TOF ratio of 0.9 (50). Caldwell et al. showed a decrease in TOF ratio with a neostigmine dose of 40 μg/kg, but not after 20 μg/kg, when using neostigmine after the TOF ratio had already recovered almost to unity [23]. Recent data have suggested that this paradoxical effect could be clinically relevant and may adversely affect postoperative pulmonary outcome [24]. However, a secondary analysis revealed that the appropriate use of neostigmine, i.e., dosing based on neuromuscular monitoring, reduces postoperative complication [25]. Moreover, Murphy et al. have shown that 40 μg/kg neostigmine given at either a TOF ratio of 0.9 or even 1.0 was not associated with any clinical evidence of muscle weakness [26].
- Required level of spontaneous neuromuscular recovery: Given that a TOF ratio > 0.9 is now generally accepted as a safe endpoint of neuromuscular recovery and that the effect of neostigmine to antagonize residual neuromuscular blockade reaches a plateau at doses between 40 and 70 μg/kg, then the level of spontaneous recovery when neostigmine-based reversal is initiated remains the only adjustable variable in clinical practice [6, 19]. For decades, reversal with neostigmine was initiated at the return of at least 1–2 twitch responses after TOF stimulation. However, given the issues discussed above, a rethinking of the required level of spontaneous recovery before initiating neostigmine-based reversal has occurred. Kirkegaard et al. assessed four different pre-reversal degrees of recovery to determine the time required to achieve a TOF ratio of 0.9. At the return of 1, 2, 3, or 4 tactile responses to TOF stimulation, neostigmine 70 μg/kg of neostigmine was administered, and the time to reach three different endpoints was determined (TOF ratio of 0.7, 0.8, and 0.9). They confirmed that even when neostigmine was given at the return of the fourth TOF response, the recovery interval was often longer than 15 min; see also Table 1. Moreover, up to 15% of patients did not reach a TOF ratio of 0.9 within 30 min [17]. Based on this data, even waiting for the return of the fourth response to TOF, and then waiting 15 min,

Table 1 Time interval to reach different TOF ratios after 70 μg/kg neostigmine given when 1, 2, 3, or 4 TOF responses after cisatracurium-induced neuromuscular blockade were detectable. Adapted from [17]

	TOF ratio 0.7	TOF ratio 0.8	TOF ratio 0.9
1 TOF response	10.3 (5.9–23.4) min	16.6 (8.9–30.7) min	22.2 (13.9–44.0) min
2 TOF responses	7.6 (3.2–14.1) min	9.8 (5.3 (25.0) min	20.2 (6.5–70.5) min
3 TOF responses	5.0 (2.0–18.4) min	8.3 (3.8–27.1) min	17.1 (8.3–46.2) min
4 TOF responses	4.1 (2.4–11.0) min	7.5 (3.0–74.5) min	16.5 (6.5–143.3) min

Data are median and range

TOF train of four

may result in patients presenting to the recovery room with postoperative residual block. Findings from Baurain et al. support this assumption that pre-reversal recovery should be more advanced before administering neostigmine. The investigators examined factors associated with optimal neostigmine-based reversal and proposed a pre-reversal T1 of at least 25% to obtain a TOF ratio > 0.9 within 15 min after the administration of 40 μg/kg neostigmine. Earlier administration of neostigmine led to incomplete recovery at 15 min, independently of the dose of neostigmine given [27]. Recent data from a systematic review confirmed these findings [19]. Indeed, the authors recommended delaying the administration of neostigmine until a pre-reversal T1 of at least 25% of baseline is reached or to accept a recovery interval longer than 15 min. Thus, the therapeutic range of neostigmine has become rather narrow. Shallow degrees of residual paralysis, i.e., a TOF ratio between 0.4 and 0.9, are still potentially harmful and, thus, should be avoided [28]. As mentioned previously, the ability to swallow, the hypoxic ventilatory response, and the upper airway integrity are all affected at shallow degrees of residual paralysis, corresponding to a TOF ratio of 0.8. However, these shallow degrees of residual paralysis are rather difficult to detect, at least with a simple nerve stimulator or clinical tests of muscle strength. Thus, even when all four responses after a TOF stimulation are detectable with no fade, clinically relevant residual paralysis cannot be excluded. However, in this situation, neostigmine doses between 20 and 30 μg/kg will lead to safe neuromuscular recovery in less than 10 min [29, 30]. Moreover, at these small doses, paradoxical effects of neostigmine are not likely to be expected, which supports the routine administration of reduced neostigmine doses, even when no fade is detected after TOF stimulation.

Conclusions

When neostigmine is given at the return of 1–4 TOF responses, a recovery interval over 20 min has to be expected. Increasing the dose of neostigmine beyond 70 μg/kg will not further accelerate this recovery interval, but it may paradoxically increase the risk of adverse events. Shorter recovery times after neostigmine administration are obtained when reversal is initiated at more advanced levels of spontaneous recovery. Reduced doses of neostigmine are effective to antagonize those shallow, but still potentially harmful degrees of neuromuscular recovery.

Compliance with Ethical Standards

Conflict of Interest Pierre-Eduard Lorrain has received compensation from Merck for service as a consultant.

Denis Schmartz declares that he has no conflict of interest.

Thomas Fuchs-Buder has received compensation from Merck for service as a consultant.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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