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Dosing, Monitoring, and Reversal of Neuromuscular Blockade: Are Anesthesiologists Following Evidence-Based Practices?

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Abstract Paralysis is an integral component of many balanced anesthetics, and appropriate dosing, monitoring, and reversal of paralytic agents are important aspects of anesthetic care. Recommendations for all three have been well-described in the literature, yet the literature is also replete with evidence that providers often do not follow published guidelines, and that patients suffer with residual paralysis with subsequent serious or catastrophic sequelae. We discuss appropriate evidence-based techniques for dosing, monitoring, and reversal of paralytic agents, and barriers to implementation of best practices.

Keywords Residual paralysis · Neuromuscular blockade · Acetylcholinesterase inhibitor

Introduction

Paralysis for surgical procedures became a commonplace after the introduction of a number of relatively safe neuromuscular blocking agents in the mid-20th century. Prior to the introduction of these medications, immobility during surgery was provided by the muscle relaxant properties of volatile agents. The high concentrations of volatile agents are needed to provide relaxation, however, was complicated with hemodynamic depression, and paralytics allowed for the introduction of "balanced anesthetic technique", which allowed a combination of medications to provide ideal surgical conditions without the unwanted side effects of any one drug alone.

As new paralytics were introduced into the anesthetic armamentarium, so too were new monitoring devices which yielded significant information regarding paralytic pharmacodynamics and the unique properties of neuromuscular recovery. Recommendations for monitoring were well-described in the literature and anesthetic texts from the 1970s onwards described details of single twitch, train of four (TOF), double-burst suppression, post-tetanic potentiation, and sustained tetanus monitoring. Indeed a right of passage of any student of anesthesia included a mandatory lecture, usually early in training, describing the percent of receptors bound at each level of train of four recovery, and appropriate timing for administration of reversal agents [1]. Despite well-established information, standardized education, and clinical experience during training, however, many anesthesia providers (self-admittedly) do not follow evidence-based recommendations, despite awareness of literature to the contrary [2•]. This manuscript will review the evidence for appropriate monitor-based medication dosing and reversal, and discuss potential barriers to the implementation of best practices.

Onset of Paralysis

Unlike many other medications, paralytics are initially dosed at supratherapeutic concentrations in order to achieve rapid onset of clinical effect. Dosing at twice to three times the ED95 for non-depolarizing agents is the norm, and while neuromuscular monitoring may be appropriate at the start of a case, most providers trust in the

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pharmacodynamic properties of these drugs, and intubate after a set time period has elapsed. Due to these predictable pharmacodynamics, excellent intubating conditions are generally achieved, and monitoring is felt by many to be superfluous at this time point.

Maintenance of Paralysis

Appropriate redosing of paralytic agents should occur when patients demonstrate some spontaneous recovery of neuromuscular function. Maintaining one to two twitches (during TOF monitoring) is the goal for providing ideal surgical conditions, and this can generally be achieved by giving a small ED50–ED95 dose of paralytic every 20–40 min during the maintenance phase of anesthesia; although there is a growing body of evidence that deep neuromuscular blockade (TOF 0–1) may indeed provide optimal surgical conditions in laparoscopic surgery [3•]. Indeed many providers practice in precisely this way, using time-based dosing rather than monitor-based dosing, despite a clear understanding that inter-patient and inter-anesthetic variability is high. Surveys of clinicians in Germany and the United Kingdom reveal that only 28 and 10 % respectively, use neuromuscular monitors of any kind, which suggests that those that do not use monitors achieve good results nonetheless [4, 5].

Proper monitoring should involve TOF examination at the adductor pollicis muscle, and indeed the majority of data published in basic texts (describing onset, duration, fade, and recovery characteristics) specifically cite thumb data. At times, however, the hand may not be available or suitable for monitoring (when the arms are tucked, for instance), and the facial nerve can be monitored instead, although we understand that certain caveats should be kept in mind when monitoring in that location. First, inappropriate lead placement can lead to direct muscle stimulation which can be inappropriately interpreted as neuromuscular recovery. Second, while facial nerve function closely parallels diaphragmatic and glottic muscle function, ulnar nerve recovery more closely predicts complete recovery from paralysis. Thus, patients undergoing facial nerve monitoring may suffer from incomplete recovery or be incorrectly deemed "reversed" when they still have measurable paralysis in the hand. In fact, it has been shown that patients that are monitored with facial nerve stimulation had a fivefold increased risk of residual paralysis when compared to those monitored at the ulnar nerve [6]. Unfortunately despite these limitations, many providers choose to monitor the facial nerve for reasons of pure convenience, despite having access to the hand. Furthermore, clinical decisions may be based on facial nerve monitoring and extrapolated to adductor pollicis recovery…again a situation which may lead to incomplete recovery.

Recovery from Paralysis

As previously described, introduction of paralysis is generally done without neuromuscular monitoring, and maintenance of paralysis frequently occurs with a complete or relative lack of appropriate functional data. At the completion of an anesthetic, appropriate reversal of neuromuscular blockade is mandatory. Reversal is typically given at the time of some degree of spontaneous recovery, and dosing of reversal agents is either weight or time based, or a combination thereof. Unfortunately, again, many anesthesia providers fail to monitor for recovery at the conclusion of a case. A 2010 survey completed by Naguib and colleagues revealed that 19.3 % of European and 9.4 % of American respondents never use neuromuscular blockade monitors at the time of reversal [7]. Most respondents reported that neuromuscular blockade monitors should not be used as part of *standard* monitoring during anesthesia despite a clear understanding of the importance of neuromuscular recovery.

Providers display a willingness to rely on clinical signs, such as respiratory pattern or measurement of oxygen saturation to determine when patients can be safely extubated, although measurements of vital capacity, negative inspiratory force, or minute ventilation breathing all require patient participation to be reliable and all can be normal in the face of significant residual neuromuscular weakness. Furthermore, clinical tests of strength including head lift and grip strength are subjective, and also have been shown to not correlate with complete recovery [5, 8••].

Dosing of reversal agent also seems to be variable, with some providers considering 0.05 mg/kg to be a "maximum dose", while others use 0.07 mg/kg. Some give the maximum dose to all patients regardless of degree of paralysis at the time of reversal, while others vary their dose depending on recovery. While 0.07 mg/kg is described in the literature as a maximum dose, care must be taken when giving patients high doses of cholinesterase inhibitors in the face of light block…the neostigmine alone can cause weakness when overwhelming doses are given [9]. A more prudent approach would be to use 0.05 to 0.07 mg/kg when patients have 3–4 twitches visible on TOF monitoring at the hand (with fade), and 0.025 mg/kg when patients have 4 strong twitches with no evidence of fade [10, 11]. Note that care should be taken when attempting to reverse patients at only 1 twitch, as recovery can take >20–30 min, even with maximum neostigmine dosing [12].

Clinical Implications of Residual Paralysis

Residual paralysis, defined as having a TOF ratio less than 0.9, occurs in 30–50 % of patients receiving intermediate acting agents, and use of intraoperative monitoring decreases that risk [13]. Incomplete recovery from paralysis results in an increased risk for critical pulmonary complications in the PACU, a subjective complaint of weakness, and a decrease in satisfaction with anesthetic recovery [14, 15]. Failure to reverse neuromuscular blockade has also been shown to increase risk of mortality or coma by 90 % within 24 h of surgery [16]. Yet despite these figures, many clinicians continue to monitor and reverse casually or inappropriately.

Many clinicians point out that despite data to the contrary, they don't see their patients having weakness-associated adverse events, and to that point, the vast majority of our patients, despite some having residual paralysis, recover uneventfully and are discharged with no untoward events, lending support to commonly practiced monitoring/reversal techniques [2, 5]. It must be pointed out, however, that not all patients are created equally, and obese/elderly/pediatric/frail patients are at a uniquely increased risks of weakness-associated adverse events, and many adverse events that have no clear causation can retrospectively be attributed to residual paralysis [17].

Monitoring and Reversal of Neuromuscular Blockade: Evidence-Based Recommendations

We therefore conclude the following from the preceding discussion:

(1) Evidence for appropriate dosing, monitoring, and reversal of neuromuscular blocking agents is well-established in the literature.
(2) Despite this evidence, many providers do not follow evidence-based guidelines for reasons of habit or "experience".
(3) Residual paralysis occurs frequently, but adverse events do not. Nevertheless certain high-risk patients are clearly at a higher risk of suffering from postoperative complications when residual paralysis is present.
(4) Simple evidence-based guidelines should be promulgated by academic and specialty societies to improve safety of anesthetic care, and compliance with best practices should be measured and reinforced.

Appropriate evidence-based recommendations, therefore, should include the following:

(1) All patients receiving non-depolarizing neuromuscular blocking agents must be monitored for neuromuscular function.
(2) When possible, TOF monitoring should occur at the ulnar nerve. If facial nerve monitoring is necessary, then special care must be taken to ensure complete recovery prior to extubation.
(3) Patients with 1, 2, or 3 twitches (visual or tactile) at the conclusion of surgery should receive a "full dose" of reversal agent (50–70 mcg/kg), with the understanding that full reversal will not occur for 15+ min.
(4) Patients with 4 twitches (visual or tactile) at the conclusion of surgery should receive 30–50 mcg/kg of reversal agent, again with the understanding that full reversal will not occur for at least 7 min.
(5) Patients with 0 twitches, or those with 0 twitches but post-tetanic potentiation should *not* receive anticholinesterase reversal until spontaneous recovery has occurred.

Conclusion

The etiology of weakness and weakness-related respiratory events in the PACU is multifactorial, with patient, surgical, and anesthetic factors all coming into play. Clinicians should follow time-tested and evidence-based recommendations to prevent paralysis-related events. The Association of Anaesthetists of Great Britain and Ireland have issued a statement in 2015 mandating that a peripheral nerve simulator must be used whenever NMB drugs are given [8]. We urge the American Society of Anesthesiologists to follow this lead and include peripheral nerve stimulation/monitoring to monitoring standards when paralytics are given.

Compliance with Ethics Guidelines

Conflict of Interest Moumen Asbahi and Roy Soto declare that they have no conflict of interest.

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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