Reversal of Neuromuscular Blockade

"Identification Friend or Foe"

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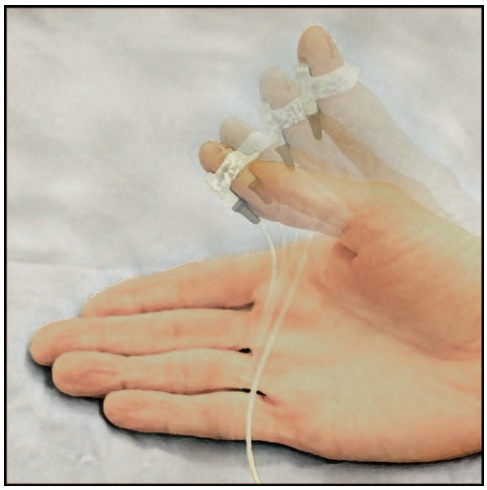
"On that memorable Sunday morning in September 1939, while the Prime Minister was broadcasting to the Nation, and telling us that we were at war with Germany, a single French aircraft flew over the Channel. It could not be identified, so it was assumed to be hostile; the sirens sounded for the first time, and everyone went into an air raid shelter."

—Lord Bowden[1]



"The depth of block cannot be guessed, inferred, or 'assessed' by subjective means, regardless of one's vast clinical experience ..."

THE article by McLean *et al.*[2] builds on a burgeoning body of literature that for more than 50 yr has described potential complications associated with the use of neuromuscular-blocking agents (NMBAs). There seem to be two themes: The first irrefutable finding is affirmation that the use of NMBAs is associated with postoperative residual weakness that may lead to significant morbidity and, rarely, mortality. Although the second theme is also supported by good science, it is more controversial as it appears to "fly in the face" of the typical anesthesiologist who feels that administration of neostigmine to induce pharmacologic reversal is routinely and reliably sufficient to ensure adequate postoperative neuromuscular function (and thus avoid respiratory complications). However, both the anesthesia and the critical care medicine literature is replete with studies documenting that with or without neostigmine, a significant proportion of our patients exhibits significant residual neuromuscular block (defined as train-of-four [TOF] ratio <0.90) when tested objectively in the postanesthesia care unit (PACU).[3]

In a sense, NMBAs are similar to opioids—they are both "life-saving" and "complication-producing" drugs. When used appropriately, NMBAs allow the performance of surgical procedures that would be much more difficult and sometimes impossible without the induced paralysis. Similarly, opioids allow the performance of surgical procedures that would otherwise induce a more significant physiologic trespass with increased risks and complications. But both NMBAs and opioids have significant, sometimes deadly, side effects unless monitored appropriately. Monitoring the depth of analgesia and respiratory depression produced by opioids can be difficult, inexact, and unreliable. Unlike opioids, however, the depth of neuromuscular block, and the adequacy of reversal, can and should be measured—easily, predictably, and routinely. We have the technology, and we have the proof—so far, we have just not had the resolve.

It is inexplicable that monitoring of the depth of NMBA block and adequacy of pharmacologic reversal are still not used routinely, and several previous editorials have pointed out the lack of understanding of clinicians of, and perhaps interest in, neuromuscular monitoring.[4,5] Why should this be? We believe that a host of factors[6] provide some explanation and should include medical heuristics. These heuristics are mental shortcuts used to assist our everyday decision-making during patient care, but in essence these are educated

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guesses based on experience, trial-and-error, and pattern recognition (*e.g.,* "rocuronium is always reversible 1 hour after intubation"). They are a quick alternative to the vigorous analysis of data (*i.e.,* routine quantitative TOF monitoring to determine readiness and dosing of NMBA reversal agents). This heuristic decision-making is not only common, useful, and efficient but also prone to a number of unconscious influences characterized as cognitive errors.[7]

How might these heuristic-driven cognitive errors impact our anesthesia practice? *Confirmation bias* occurs when clinicians selectively accept subjective data ("the patient had a good hand squeeze") to support a desired or anticipated hypothesis ("I expect full recovery of neuromuscular function after neostigmine"), while simultaneously ignoring information we do not find consistent with our hypothesis (*i.e.*, the plethora of literature documenting the poor reliability of clinical signs to validate complete reversal of NMBA drugs). Confirmation bias often compounds an *anchoring bias*, whereby the clinician also uses confirmatory data ("the patient has a good hand squeeze") to support their anchoring hypothesis ("all my patients do fine in the postanesthesia care unit [PACU] because I am a good anesthesiologist with experience and expertise"). The temptation to rely on heuristics is amplified by *production pressure* and past success (explained in part by the relatively rare incidence of significant morbidity from inadequate neuromuscular reversal). But success has its liabilities, and it can be blinding. Recurring "success" breeds complacency that can easily follow weeks or even months of uneventful general anesthetics with (apparently) routine reversal of NMBAs and uneventful extubation of the trachea, followed by angst, confusion, and doubt when a healthy patient requires urgent reintubation due to residual muscle weakness just minutes after arrival in the PACU.

The investigation by McLean *et al.*[2] adds important additional insights to our growing body of knowledge about residual muscle weakness in the PACU[8,9] and is clinically relevant from several perspectives. First, it reestablishes the well-known and time-tested efficacy of anticholinesterases: "appropriate neostigmine reversal" (defined as "neostigmine ≤60 μg/kg given at a TOF count of ≥2") markedly decreased (by 79%; CI, 69 to 92%) the "dose-dependent association between NMBAs and respiratory complications." Second, it underscores that the use of higher doses of intermediate-acting NMBAs is associated with an increase in the risk of postoperative pulmonary complications of 28% (CI, 4 to 57%). In fact, in patients at particular risk for respiratory complications (*e.g.*, those undergoing laparoscopic cholecystectomy), the association between high doses of NMBA used intraoperatively and postoperative pulmonary complications was significant (highest NMBA dose quintile *vs.* lowest NMBA quintile odds ratio was 3.42; CI, 1.01 to 11.57). Third, no particular agent or class (aminosteroid *vs.* benzylisoquinolinium) was protective of the risk of pulmonary complications, which highlights the fallacy that one or another NMBA may be preferred because it is more "reliable."

Fourth, McLean *et al.*[2] provide some seemingly paradoxical findings regarding the practice of reversing NMBAs. We learn that the use of neostigmine under certain conditions is dose-dependently associated with an increased risk of postoperative pulmonary complications. But in reality, this increase in the strength of the association between greater neostigmine doses and more frequent postoperative pulmonary complications is consistent with previous reports[10] and with observations in clinical practice: Higher doses of intraoperative NMBAs are assessed by clinicians (in most cases, by subjective evaluation)[11,12] to require greater doses of neostigmine, which, especially if administered at either extreme of the recovery curve (*i.e.*, at deep block, say TOF count <2) or at near-complete recovery (say, TOF >0.40), may result in residual neuromuscular block. At the lower end of the recovery spectrum (*i.e.*, profound block), traditional anticholinesterase inhibitors such as neostigmine are incapable of producing sufficient recovery because of their ceiling effect.[13,14] At the other end of the spectrum, excessive doses of neostigmine during minimal block (or no block) may result in an apparent paradoxical interference with normal neuromuscular function, particularly of the upper airway and pharyngeal muscles.[15] In either case, the clinical results for the patient are suboptimal.[16] These findings again illustrate how heuristics-driven decision-making based on either the clinical experience of anesthesiologists or even on simple clinical parameters (tidal volume, vital capacity) or clinical tests (grip strength, 5-s head lift) usually result in residual neuromuscular weakness in 20 to 40% of patients.

So, what is the clinician to do? On the one hand, clinical experience-guided management of neuromuscular block (in other words, subjective evaluation of clinical signs of neuromuscular block and recovery, along with the management of NMBA therapy based on averaged pharmacodynamic data such as duration since last administration of NMBA) has served many patients fairly well much of the time. But we now understand that the consequences of residual weakness must be measured in ways far more sensitive than the rate of tracheal reintubations in the PACU.[17] To that goal, other editorials and letters have already called for specialty organizations' development of guidelines of perioperative monitoring of the effects of NMBAs (and their reversal), and in the past decade, several countries, including Australia, the Czech Republic, Denmark, Germany, and France, have developed and published such clinical guidelines. We embrace these efforts and applaud the American Society of Anesthesiologists leadership for currently grappling with this same issue.

In summary, the lessons for providers are powerful reminders to optimize our patients' safety: (1) the decision to administer NMBAs should not be taken lightly and should be made only when clinically necessary; (2) increasing the total dose on NMBA increases its total duration of action and the likelihood of residual neuromuscular block and related sequelae; (3) residual neuromuscular block is associated with real, not insignificant, postoperative pulmonary

complications (respiratory failure, pulmonary edema, tracheal reintubation, and pneumonia); (4) pharmacologic reversal (neostigmine) based on the objective-evoked responses (*i.e.*, measured) is associated with the decreased risk of postoperative pulmonary complications; (5) in the absence of measured evoked responses, empirical reversal with neostigmine at either extreme of the recovery curve is associated with an increased risk of pulmonary complications. In light of the aforementioned findings, the obvious clinical recommendation was, is, and will continue to be: let the timing and dosing of both NMBAs and anticholinesterases be guided by objective measurement of neuromuscular-evoked responses. Objective measurement of neuromuscular function is mandatory. The depth of block cannot be guessed, inferred, or "assessed" by subjective means, regardless of one's vast clinical experience—in other words, we should always use objective monitoring technology to identify NMBAs (and for that matter, neostigmine) as either "friend or foe."

Competing Interests

Dr. Brull is a member of the Anesthesia Patient Safety Foundation (APSF) (Indianapolis, Indiana) Executive Committee and Board of Directors and shareholder in ADBV (Amsterdam, The Netherlands), a medical device company. Dr. Prielipp is a member of the APSF Executive Committee and Board of Directors.

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