REFERENCES

Train-of-Four To Monitor Neuromuscular Blockade?

ICU-acquired weakness is an unfortunately common and serious occurrence among critically ill patients. ICU-acquired weakness has multiple causes but is generally attributed to the following three conditions: ICU-acquired myopathy; ICU-acquired weakness; and prolonged neuromuscular blockade. The latter two conditions may be attributable to the use of neuromuscular blocking agents (NMBAs). Monitoring of the depth and duration of chemical paralysis is important to optimize neuromuscular blockade for each individual patient and to avoid complications of therapy. In a 2002 clinical practice guideline, in previous guidelines, and in other reviews, the use of peripheral nerve stimulation testing by periodically evaluating the response to a “train-of-four” (TOF) stimulation is recommended, in combination with clinical assessment, for all patients receiving NMBAs. However, the added value of TOF monitoring has been critically examined in only a few controlled trials that directly compare TOF testing with clinical evaluation alone, and these studies have arrived at contrasting conclusions. In this issue of CHEST, Baumann and colleagues report the results of a single-center randomized, controlled trial that prospectively compared the titration of cisatracurium by TOF monitoring to clinical evaluation alone. They found no difference in recovery time after the cessation of NMBa administration or in the total NMBa dosage given. No cases of ICU-acquired weakness were observed. They concluded that TOF testing is unnecessary when careful clinical assessment is performed, but they limit this recommendation to patients who are receiving the agent they used, cisatracurium, and a related agent, atracurium. The evaluation of neuromuscular blockade begins with the indication for therapeutic paralysis and the desired level of muscle relaxation. Although common indications include the control of intracranial pressure, the control of muscle spasm, the control of intractable agitation, and the reduction in oxygen consumption, the majority of patients, including those in the study by Baumann et al, receive NMBAs to optimize patient-ventilator synchrony and potentially to improve oxygenation. The depth of neuromuscular blockade that is necessary to achieve the desired clinical goals, which range from synchronous respiration, to apnea, or even complete paralysis, varies considerably. The goals of monitoring include measures of effectiveness (ie, how well we are achieving our clinical goals), as well as safety (ie, whether we are avoiding overdosage), and otherwise reducing the likelihood of prolonged neuromuscular blockade and/or ICU-acquired myopathy. Although both the clinical assessment and measurement of the TOF are routinely utilized, survey data from 10 to 15 years ago indicated the use of TOF monitoring in only 8.3 to 41% of ICUs.

All patients who receive NMBAs should undergo periodic clinical assessment, but what exactly is meant by this term? Experts consider the observation of skeletal muscle movement and respiratory effort as the foundation of clinical assessment. Clinical evaluation could more precisely focus on the assessment of the adequacy of muscle relaxation to achieve specific goals (ie, the observation of synchronous breathing, apnea, or absence of movement) as measures of efficacy. In the study by Baumann et al, clinical assessment consisted of evaluating patient-ventilator dysynchrony, including “bucking” the ventilator or high peak airway pressures, which prompted the increasing of the NMBA dosage. Apnea was not the goal except in patients undergoing inverse ratio ventilation, and the frequency of the
use of this modality was not stated. In other prospective studies that were designed to compare clinical assessment to TOF, Strange et al\textsuperscript{10} considered “best clinical assessment” to be ventilator synchrony and the absence of clinical movement, and Rudis and colleagues\textsuperscript{9} considered “clinical efficacy” to be the absence of movement or spontaneous breathing. Since deep tendon reflexes (DTRs) disappear as 100% blockade is achieved,\textsuperscript{13} the routine testing of DTRs could be incorporated into the clinical evaluation. Clinical assessment also might include specific dose-reduction titration strategies. For example, Strange et al\textsuperscript{10} mandated that at least once every 12 h the atracurium infusion rate be reduced to allow patient movement, after which patients were maintained in a slightly higher state of paralysis. Rudis and colleagues\textsuperscript{9} required titration to the minimum effective dose by decreasing the vecuronium infusion rate every 2 to 3 h until the patient was breathing above the preset ventilatory rate, then increasing the infusion by 0.02 mg/kg/h. Baumann et al did not specify a strategy, per se. None of these studies\textsuperscript{9,10} incorporated a formal “drug holiday” strategy in which the drug infusion was stopped daily. This technique permits the periodic evaluation of the neurologic status, reassessment of the ongoing need for neuromuscular blockade, and assessment of the adequacy of analgesia and sedation, and should reduce the accumulation of the drug and active metabolites. The use of daily NMBA interruption has been recommended in some guidelines and reviews,\textsuperscript{1–3} but is based solely on expert opinion.

There are numerous techniques that are designed to test the depth of neuromuscular blockade using peripheral nerve stimulation; however, the TOF approach is considered to be the easiest and most reliable method for the ICU setting.\textsuperscript{1} Four equal electrical charges are delivered every 0.5 s from the nerve stimulator device that is attached to leads overlying a superficial nerve, usually the ulnar or facial nerve, and the contraction of the innervated muscle (i.e., the adductor pollicis or orbicularis oculi muscle, respectively) is graded subjectively by palpation or observation. Guidelines\textsuperscript{1} support the titration of NMBA, so that one to two of four twitches are present, as Baumann and coworkers did.

What is the evidence that TOF testing improves outcomes? Investigators have reported\textsuperscript{16,17} that the implementation of practice guidelines that include the routine measurement of TOF is associated with fewer episodes of prolonged weakness compared to the baseline period. However, three prospective trials have provided the best evidence.\textsuperscript{9,10} Rudis and colleagues\textsuperscript{9} randomly assigned 77 patients who received vecuronium by continuous infusion to TOF monitoring (goal, one of four twitches) or clinical assessment. Patients assigned to TOF testing required less vecuronium, had more rapid recovery to four of four twitches and to spontaneous breathing, and had fewer episodes of “delayed recovery” (i.e., defined as > 4 h from drug discontinuation to four of four twitches) after an infusion averaging 50-h duration. They noted that renal dysfunction, which was present in 20% of patients, was strongly predictive of slower clinical recovery. Four of the 42 patients (TOF group, 1 patient; control group, 3 patients) who underwent thorough neurologic examinations before and after receiving vecuronium had prolonged weakness lasting until death, which was likely due to acute myopathy, or hospital discharge.\textsuperscript{9} The authors subsequently estimated a cost savings of $738 per vecuronium-treated patient with TOF testing.\textsuperscript{13} In a prospective, but nonrandomized study of 36 patients who received continuous atracurium, Strange et al\textsuperscript{10} found no difference in the total dosage or recovery time between the TOF testing group (goal, three of four twitches) and the clinical evaluation group. Recovery time averaged < 1 h in both groups despite an average of 125 h of atracurium infusion. No episodes of prolonged weakness or myopathy were observed. Finally, Baumann and colleagues randomized 30 patients who received continuous cisatracurium to undergo TOF testing (goal, one to two twitches) or clinical evaluation, demonstrating no difference in total dosage or recovery time. Recovery times averaged < 1 h despite an average of 61 h of cisatracurium infusion, and no episodes of prolonged paralysis (i.e., fewer than four of four twitches at 3 h after infusion cessation) or acute myopathy were reported.

How does one reconcile the different results from these prospective trials? Although some differences in study design, target TOF, clinical dosing, and evaluation are apparent, the most likely explanation lies with the NMBA tested. The benzylisoquinolinium agents, atracurium and cisatracurium, are metabolized by Hofmann degradation, an end-organ-independent process, to inactive metabolites. Prospective clinical trials\textsuperscript{19–22} for the use of atracurium and cisatracurium in ICU patients have documented mean recovery times to 70% TOF (i.e., the amplitude of fourth twitch > 70% of amplitude of first twitch [a standard marker of recovery in research]) of 46 to 57 min and 45 to 75 min, respectively. Interestingly, even when intentionally dosed to achieve zero of four twitches, the recovery time for cisatracurium averaged only 75 min despite the administration of 50% higher doses than those used to achieve a goal of two of four twitches.\textsuperscript{22} By contrast, in a randomized, controlled trial of vecuronium vs cisatracurium, 70% TOF averaged 387 min with vecuronium, vs 68 min for cisatracurium, and
delayed recovery (ie, \(> 2\) h) was observed in 13 of 30 vecuronium-infused patients vs only 2 of 22 cisatracurium-infused patients.\(^{21}\) It is noteworthy that delayed recovery occurred despite the titration of vecuronium to a TOF of \(\approx 1\).\(^{21}\)

Prolonged neuromuscular blockade with vecuronium has been well-described.\(^{23–25}\) Vecuronium is an aminosteroid, related to pancuronium, that undergoes hepatic hydrolysis to three metabolites, of which 3-desacetyl-vecuronium is estimated to be 50 to 80% as active as the parent compound and accumulates in patients experiencing renal failure.\(^{1,20}\) Segredo et al\(^{21}\) previously documented a strong relationship between plasma 3-desacetyl-vecuronium levels and prolonged neuromuscular blockade and/or myopathy. Additionally, up to 35% of a vecuronium dose is renally excreted, 50% is excreted in bile,\(^1\) and drug clearance changes in an unpredictable fashion during prolonged infusion.\(^{27}\) A correlation between prolonged neuromuscular blockade and renal insufficiency has been documented in many studies,\(^9,17,23\) but not all.\(^{21}\) Accordingly, the current recommendations support using atracurium or cisatracurium instead of vecuronium or pancuronium in patients who have renal or hepatic dysfunction.\(^{1,2}\)

Acute quadriplegic myopathy syndrome (AQMS) is a devastating cause of ICU-acquired weakness that has been attributed to the prolonged use of NMBAs, usually in the setting of concomitant corticosteroid administration.\(^{1,2–16,24,28}\) AQMS is characterized by prolonged weakness of the limb and trunk muscles with sparing of the extraocular musculature. Abnormal compound motor action potentials but generally intact sensory nerve conduction is found on testing.\(^{29}\) There is evidence for the following two mechanisms as its cause: (1) widespread myonecrosis that may result in elevated serum creatine phosphokinase levels\(^{30,31}\); and (2) selective myosin loss that is accompanied by marked reductions in myosin messenger RNA.\(^{32}\) Originally reported to occur with the aminosteroid agents pancuronium and vecuronium,\(^{30,32,33}\) an association with benzylisoquinolinium agents also has been reported in case reports.\(^{28,32,34,35}\) Interestingly, in a number of controlled trials AQMS was not reported following atracurium or cisatracurium infusion in > 200 cases, compared to 5 of 107 cases of vecuronium-infused patients.\(^{9,10,19–22}\) It appears that the avoidance of overdose using TOF-based drug titration is not protective since most of the more recently reported cases of AQMS developed despite TOF monitoring.\(^{9,21,34,35}\)

There are potential technical and interpretative problems with TOF testing.\(^{1,36}\) The presence of perspiration or tissue edema can interfere with nerve stimulation, and direct muscle stimulation can misleadingly result in muscle contraction despite effective chemical blockade.\(^{36–38}\) Variations in management such as visual vs palpation assessment, and the use of facial vs ulnar nerve stimulation likely reduce the consistency of interpretation.\(^{39}\) Finally, thermal injury has been described.\(^{38}\) The training of ICU nurses regarding TOF is widely performed,\(^{14}\) and should improve the accuracy and reliability of testing. TOF testing requires additional time to perform,\(^{18}\) and may not be consistently performed, interpreted, and documented.

Despite these limitations and limited evidence,\(^{37}\)
TOF testing has achieved broad acceptance because of expert recommendation, its relative simplicity and low cost, its low risk, and its incorporation into successful strategies for managing neuromuscular blockade. The simple numerical score enhances clarity and improves communication among caregivers. Thus, the removal of TOF testing from the box of ICU-monitoring tools, even for selected cases as suggested by Baumann and colleagues, requires careful consideration. Given the unreliable recovery profile of vecuronium, the use of TOF testing, in concert with clinical assessment, would improve dosing, shorten the recovery time, and reduce the likelihood of complications in this setting and is thus recommended. In contrast, the added value of TOF testing to clinical assessment during atracurium or cisatracurium blockade is unproven for preventing delayed recovery or AQMS, or even for reducing the dosage of drug administered.

It is likely, however, that TOF testing would allow more precise dosing, even for atracurium and cisatracurium, when deep neuromuscular blockade (ie, for apnea or complete paralysis) is performed and clinical assessment is less reliable. Reliance on clinical assessment alone would highlight some practical issues. As noted above, there is considerable variability and subjectivity in performing, interpreting, and documenting a periodic clinical assessment, and thus standardization of the evaluation among caregivers would be important. Simplicity and clarity of documentation, similar to that for TOF testing, would also be useful. Finally, it would be important to confirm that the elimination of TOF testing, as an additional safety measure, did not inadvertently reduce the vigilance with which these critically ill and complex patients are monitored. Recommendations for the administration of NMBAs to ICU patients are offered in Table 1, recognizing that many are based primarily on expert opinion or limited data. Baumann and colleagues are to be commended for challenging the status quo with their well-done prospective study. Further research is needed to optimize our use of these valuable but potentially hazardous drugs, and to develop strategies to prevent AQMS and/or recognize it an early stage.

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Off Label, On Target?

In the lexicon of current medical practice, the term off-label is immediately understood through all levels of the profession. It refers to the use of a medication for a disease, or a dose, or method of administration that is not listed in the official labeling of its use. It is not only commonplace, but in some cases may represent the preferred therapy. On the other hand, the basis for off-label use may have the shakiest of support if using the evidence-based pyramid. Treatment is often based on anecdotes or small case series, although some therapies will have withstood the scrutiny of a randomized double-blind investigation. By its very nature though, off-label use represents extrapolation from prior experience and, more often than not, represents the early application of a yet-unproven therapy. It is important to note that this practice may not be inappropriate or ineffective, just unproven. The questions that naturally arise in this scenario span several areas, including concerns about safety, ethics, and responsibility.

On the other hand, the practice of medicine is replete with examples of treatment that strayed from usual or standard practice, only to subsequently be demonstrated as a viable or preferable option. Sildenafil in the treatment of pulmonary hypertension may be the latest example, but some may recall that at one time isoniazid also was used to treat depression. The phenomenon of off-label use is not restricted to medications. There are treatments and procedures that also fit this categorization, as the application of effective therapies is extended to other similar, but distinct conditions. This is demonstrated by the increasing use of hyperbaric oxygen therapy or noninvasive ventilation in a host of conditions similar but disparate from those in the initial investigations. Of course, the evidence to support these variations in management may be difficult to accumulate or may occur several years after the procedure has been in place. It is unrealistic to expect the “gold standard,” randomized, placebo-controlled trial for every realm of medical care. There simply is not enough time, money, or investigators. It follows that success in one arena might lead to application in other similar, but distinct conditions.

In this issue of CHEST (see page 1281), Wongsurakiat and colleagues present data that highlights this very process. They document a change in ven-