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Neuromuscular blocker studies of critically ill patients

According to surveys of intensive care units (ICUs) at the beginning of the 1990s, the most common indications for neuromuscular blockers (NMBs) are to facilitate mechanical ventilation during respiratory failure, reduce oxygen consumption, prevent shivering and control intracranial hypertension [1, 2]. In the decade following these reports, the advent of propofol and the use of benzodiazepine and narcotic infusions have relegated paralysis to a final option for critically ill patients. This practice is strengthened by the severe morbidity of critical illness myopathy as a sequela to NMB use [3].

In this issue of Intensive Care Medicine, Lagneau et al. [4] present the results of a multi-center examination of paralysis on the end-inspiratory plateau airway pressure (EIPAP) during acute respiratory failure (PaO2/FIO2 <200). Patients were administered infusions of cisatracurium to maintain train-of-four (TOF) ratios of 0/4 or 2/4 at the orbicularis oculi. A significant increase in oxygenation and reduction in EIPAP were found with both partial and complete paralysis during the 2h study period. The total amount of cisatracurium infused was lower and the recovery was faster with TOF 2/4 compared with 0/4. There are several points that should be considered for this investigation and, in general, studies of NMBs in critically ill patients.

The standardization of the patient population is the most fundamental issue and is a difficult task. Intensivists, confronted with patients with multi-system organ failure and sepsis, administer a wide range of drugs that may augment the blockade at the neuromuscular junction, increase the relative concentration of the NMB in the plasma and have more profound effects secondary to physical deconditioning [5, 6, 7, 8, 9, 10]. Neuromuscular blockade for respiratory failure secondary to chronic obstructive pulmonary disease may be potentiated by the presence of altered muscle contractile properties [11]. These issues are all considered as exclusions in NMB studies outside of the ICU [12]. The dose of NMBs in practice is based on a clinical response such as the TOF. For calculations of these drugs on a milligram/kilogram basis, the ideal body weight [12] is a more accurate reflection of muscle mass than total body weight. Therefore, the use of total body weight may confound any comparison of the amount of drug used in different studies. The groups used by Lagneau and his co-investigators [4] were a heterogeneous population with respiratory failure from medical, surgical and multiple trauma causes. The duration of the neuromuscular blockade is provided, but not the concurrent medications used to treat coexisting disorders. It is likely that these patients had multiple issues since their mortality was 46% with ten of the deaths occurring in the study period.

A second key point is the determination that neuromuscular blockade is actually needed. NMBs are often given when there is an inability to ventilate a patient with rapidly deteriorating gas exchange, in order to overcome uncoordinated ventilation, tolerate inverse ratio ventilation or decrease the effects of intra-abdominal pressure upon the intrathoracic volume. The use of narcotics and midazolam were adequate to achieve this in the present study [4] since a prerequisite was synchrony with the ventilator. In order to ventilate a difficult patient appropriately, many of us would give a NMB only when an increase in the narcotic dose, a change to a more potent narcotic and/or a propofol infusion were ineffective.
Previous studies of critically ill patients used mechanomyography [9] and accelerometry [13] at the adductor pollicis after ulnar nerve stimulation to quantify TOF responses objectively. The twitch of the orbicularis oculi can be ascertained with electromyography [14]. Differences at maximal blockade have not been found among responses at the diaphragm, orbicularis oculi and adductor pollicis in normal subjects using objective measures [14]. The response at the adductor pollicis appeared to be more advantageous during recovery, since fade was present here while the activity at the orbicularis oculi was 100% [14]. The use of the adductor pollicis response in the critically ill does have its limitations, since peripheral edema may increase the resistance between the stimulus and the ulnar nerve via surface electrodes. Since estimation of the TOF response by palpation has a high degree of variability, even in experienced hands [15], the visual assessment of orbicularis oculi contractions [4] has an inherent degree of inaccuracy for partial neuromuscular blockade. It is likely that the reported maintenance of two twitches assessed by multiple investigators in many ICUs [4] had a wider degree of the depth of neuromuscular blockade than thought.

The goal of neuromuscular blockade must have a clinically relevant end point. This is easier to determine empirically in clinical practice than to demonstrate in a formal examination of multiple patients. Prior to the administration of cisatracurium, the patients in respiratory failure studied by Lagneau et al. [4] were synchronously with volume ventilation at a modest PEEP of 7.5 cmH2O. All had reasonable gas exchange with PaCO2 of approximately 45 mmHg and normal pH. The complete and partial paralysis decreased ventilator-measured EIPAP with statistical significance, but it could be argued that the clinical effect was minimal. The stable level of PaCO2 and pH during the study period indicates that the minute ventilation was unchanged and suggests that the chest wall compliance was relatively unaltered by the NMB. The increase in oxygenation after neuromuscular blockade has an unclear etiology. One explanation may be related to the study design itself. EIPAP was measured during inspiratory holds, with three measurements for each time point. This provided 24 inspiratory holds during the 2h study period that could have easily recruited additional lung units.

Even though paralysis is now employed with relative infrequency, there are still some patients who might benefit from a course of neuromuscular blockade. The lengths of stay in the ICU prior to the initiation of paralysis, the long-term improvement or decline in pulmonary function following the cessation of paralysis and the correlation between the duration of neuromuscular blockade (from 2 to 650 h [4]) and mortality are crucial subjects that merit further exploration. Future studies by Lagneau et al. [4] and other investigators may provide sufficient data for intensivists to predict the patient who will have an improved outcome following neuromuscular blockade.

References