Are Studies of Neuromuscular Blocking Drugs and Their Antagonists Unnecessarily Confusing?

There is no dearth of studies of neuromuscular blocking drugs and their antagonists. Many publications, including those from this author, have resulted from the multiple combinations of factors that may be investigated, such as different neuromuscular blocking drugs (e.g., pancuronium, vecuronium, atracurium), different antagonists (e.g., edrophonium, neostigmine, pyridostigmine), different assays (e.g., fluorometric, mass spectrometric, gas chromatographic), different muscle groups (e.g., thenar, diaphragm), different stimuli (e.g., train-of-four, single twitch, tetanic stimuli), and different recording techniques (e.g., electromyography, mechanical responses). Are these data useful in our understanding of how such drugs work and how we might best apply such drugs in clinical practice? The following observations exemplify the rationale for some of the studies and raise questions concerning the direction of future research in this area.

If two drugs have similar effects, many investigators draw parallels between the accepted mechanism of action of one drug (e.g., bungarotoxins or magnesium) and the mechanism of action of the drug in question (e.g., pancuronium or antibiotics). The success of this approach depends, in part, on the accuracy of knowledge regarding the mechanism of action of the reference drug (i.e., bungarotoxins or magnesium). For example, Singh et al. found that the neuromuscular blocking properties of the aminoglycoside antibiotics closely resemble the effects of magnesium. Because magnesium decreases the release of acetylcholine from the motor nerve terminal and postjunctional sensitivity to acetylcholine, Singh et al. concluded that aminoglycosides must have a similar mechanism of action. This conclusion is totally dependent on the accuracy of knowledge regarding magnesium. This method might be aptly called a "surrogate" approach to characterizing the mechanism of action of neuromuscular blocking drugs. The type of stimulation used in studies to elucidate the mechanisms of neuromuscular blockade is another form of such a surrogate approach. Different types of stimulation result in actions at different sites of the neuromuscular junction. In this issue of Anesthesiology, Graham et al. report that maximum depression of the first twitch of the train-of-four occurs earlier than maximum depression of the train-of-four ratio during the onset of neuromuscular blockade. However, the recovery rates for the first twitch and the train-of-four are similar. These data combined with a kinetic analysis provide indirect evidence that pancuronium acts on at least two sites of the neuromuscular junction.
The many methods of stimulation and the several neuromuscular blocking drugs available invite the execution of many experiments similar to that undertaken by Graham et al. However, the only conclusion to be derived from such studies is that the various neuromuscular blocking drugs have several sites of action. The use of such surrogate approaches to identify mechanisms of action of neuromuscular blocking drugs is unlikely to produce definitive results. In other words, methods employing various combinations of stimuli and drugs in disparate muscle groups are of limited theoretic value. More direct methods (e.g., patch-clamp and biochemical techniques) permit a more precise definition of the mechanism of action of such drugs.

However, these or similar studies may produce results of considerable clinical importance. Stimulation of a peripheral nerve is usually performed for one of two clinical reasons. First, depression of the muscle response may define the adequacy of skeletal muscle relaxation for surgery. The definition of “adequate relaxation” is obscure in many studies. Because the reason for producing the relaxation is to facilitate surgery, perhaps depression of evoked responses should be correlated with the surgeon’s assessment of relaxation. While there may be an emotional reluctance to have the surgeon assess adequacy of relaxation, there are many methods available to enhance objectivity when making subjective evaluations (e.g., blinded observer).

A second clinical reason to stimulate a peripheral nerve is because it is easy to assess the adequacy of antagonism of a neuromuscular blockade. However, studies undertaken for this reason do not always produce definitive results. For example, Rupp et al.7 and in this issue of ANESTHESIOLOGY, Kopman8 disagree on whether edrophonium provides adequate and prompt antagonism of neuromuscular blockade. In deciding whether to use edrophonium, the clinician must determine whether the Rupp et al.7 or the Kopman8 method provides the most accurate clinical prediction. Kopman8 used the evoked integrated electromyograph as the monitor of the response to single and train-of-four stimulation. On the other hand, Rupp et al.7 used mechanical strength (twitch) to monitor the response to single impulses applied to the ulnar nerve, and did not apply train-of-four stimulation. Both studies employed halothane-nitrous oxide anesthesia. Recognizing that the ability to sustain adequate ventilation is of prime importance, neither Rupp et al.7 nor Kopman8 provide the clinical correlates needed to assess the adequacy of recovery of neuromuscular function; thus, neither may allow the clinician to make a conclusion as to the usefulness of edrophonium. Indeed, few studies provide such correlates.

What method of stimulation indicates that the patient can sustain adequate ventilation, even in the presence of a stress such as airway obstruction? Although Ali et al.9,10 found a train-of-four ratio of 0.75 to be associated with adequate respiration after neuromuscular blockade from d-tubocurarine, the influence of extensive surgery and anesthesia on the relationship between the train-of-four response and adequate ventilation has not been determined. Furthermore, the relationship between various methods of peripheral nerve stimulation and tests of ventilatory adequacy (especially in the face of a stress such as airway obstruction) have not been studied with other neuromuscular blocking drugs, such as pancuronium, vecuronium and atracurium. The conclusions of Ali et al.9,10 obtained with d-tubocurarine, may not be applicable to pancuronium, vecuronium, or atracurium. Even if we did know the precise relationship between train-of-four stimulation and adequacy of ventilation, the clinician has difficulty precisely determining the train-of-four ratio by visual or tactile methods.11

What do these examples imply for future studies of neuromuscular blocking drugs and their antagonists? Perhaps the focus should be on direct rather than “surrogate” or indirect measures for ascertaining the mechanism of action of neuromuscular blocking drugs. “Adequate relaxation” needs to be defined in the context of different anesthetic states (i.e., different anesthetics and different levels of anesthesia). This is essential to determine precise dosing recommendations. The degree of antagonism of neuromuscular blockade required to assure sustained ventilation and the strength to overcome stresses such as vomiting and airway obstruction need to be defined with all clinically used neuromuscular blocking drugs. When the questions are better defined, perhaps the experimental methodology and conclusions will be less confusing.

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