Neuromuscular Pharmacology Update

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In the past 10 years, debates over the mechanisms of action of neuromuscular relaxants and their interactions with their milieu and other drugs have become less intense. Train-of-four technique has been established as the most useful method of monitoring.[1–3] Edrophonium has become widely accepted as a safe and effective reversing agent for curariform neuromuscular block.[4–5] An impressive variety of side effects of succinylcholine and complications from its use have been recognized and succinylcholine has been restricted to a specific list of indications.[6] The search for an ideal relaxant has failed to produce a safe nondepolarizing neuromuscular blocking relaxant with the rapid onset and ultra-short duration of action of succinylcholine, but has brought several excellent relaxants (atracurium, vecuronium, pipecuronium, doxacurium) to clinical use. Several others are being advanced. Meanwhile, gallamine, decamethonium and metocurine are obsolete, d-tubocurarine is losing popularity, and pancuronium is being challenged. This article is intended only to update the readers in clinical neuromuscular pharmacology, not to be an extensive review.

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I. Mechanism of Action of Curariform Drugs

The main mechanism of action of all neuromuscular blocking relaxants is receptor occupation.[7–9] Practically all neuromuscular relaxants also have prejunctional effects.[10–11] They decrease acetylcholine release or reduce its mobilization. Train-of-four fade is generally regarded as evidence of reduced mobilization by the curariform relaxants. In addition, some relaxants (especially d-tubocurarine, pancuronium, and vecuronium) have been shown to block the acetylcholine-activated ionic channels at their open configuration.[12] The contribution of channel block to the depression of neuromuscular transmission in the clinical dose range is probably insignificant. The prejunctional action of the curariform relaxants must not be confused with the prejunctional effect of magnesium or that of succinylcholine. Magnesium-induced prejunctional neuromuscular block does not manifest train-of-four fade or tetanic fade. The prejunctional effect of succinylcholine causes fasciculation.

II. Monitoring of Neuromuscular Transmission

After stimulation of the motor

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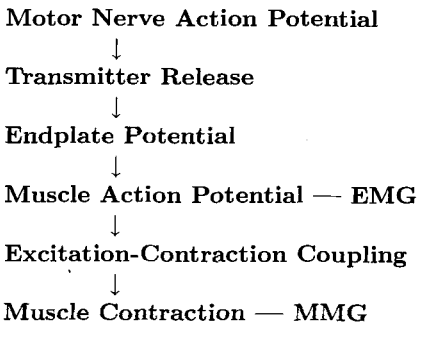


Fig. 1. Key events in neuromuscular transmission illustrating neurally evoked electromyographic and mechanical responses of the muscle.

nerve, the motor impulse is conducted to the motor nerve terminal and acetylcholine is released. Across the neuromuscular junction at the motor endplate, if the endplate potential reaches threshold, an action potential will propagate along the entire length of the muscle cell ("muscle fiber"). Once an action potential is generated, the neuromuscular transmission is complete. The rest of the neuromuscular activity includes excitation-contraction coupling and generation of mechanical force (fig. 1)[13–15] Technically, therefore, neurally evoked compound electromyogram (ncEMG) is a direct measurement of neuromuscular transmission pertinent to neuromuscular pharmacology. On the other hand, measurement of the mechanical output (mechanomyography), which may be modified by changing contractility, is more pertinent when the overall performance of the muscle is concerned, Besides neuromuscular block, many other causes of muscle weakness exist.

Measured intracellularly, the action potential is a positive signal. Measured extracellularly, the ncEMG is a negative signal. In the ncEMG, depending on the relative position of the muscle fibers and the sensing electrode, each muscle cell makes a contribution to the compound signal.

The mechanical output of the muscle contraction can be measured isometrically (in which no relative movement is allowed)[16–18] or isotonically[19] (in which the tension is held constant). Isotonically, the acceleration, the speed of motion, or the distance of travel can be measured.

Clinically, stimulation of the ulnar nerve for the contraction of the fngers, especially adduction of the thumb, is the standard and most popular method of monitoring of neuromuscular transmission.[18] The height and the speed of the finger twitch are isotonic measurements usually observed by sight. Pushing the patient's hand or finger down and holding it down will enable you to feel the changes in the patient's muscle power isometrically. In general, "feeling" (isometric estimation) is more accurate than "seeing" (isotonic estimation) the muscle power.

Various instruments and gimmicks have been proposed for neuromuscular monitoring in clinical anesthesia. Compound electromyographic instruments were electronically difficult to manufacture in the past. This should no

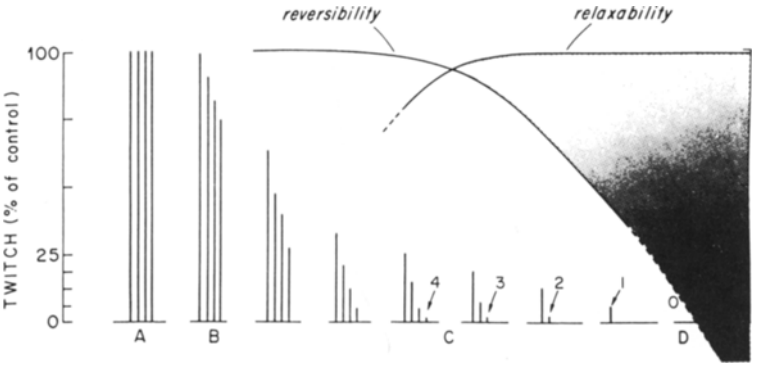


Fig. 2. Controlled relaxation using train-of-four methods. A. Control train-of-four. B. Train-of-four fade and train-of-four ratio. C. Train-of-four count. D. In the absence of any twitch, use post-tetanic count (see text).

longer be the case today. Mechanomyography is cumbersome and difficult to keep stable. Electronic accelerometry seems an excellent alternative because electronically it is easier than the ncEMG. However, for some unknown reason, the output of the accelerometry is often unstable. One major difficulty with the accelerometry is that as the finger moves, the direction, the leverage and the load of the contraction change. This reduces the fidelity of the measurement of the muscle force.

Parameters used in anesthesia practice to minitor neuromuscular transmission are twitch, train-of-four, tetanus, post-tetanic twitches, and double-burst summated twitches. The twitch provides for an ongoing basic and standby monitoring. The train-of-four is the must well-developed method of monitoring (fig. 2). Tetanus is capable of revealing a minimal degree of neuromuscular block, but it lacks specificity, consistency and quantifiability. As a result, it is no longer emphasized. Post-tetanic count is useful in very profound block when twitch, train-of-four, and tetanus are no longer elicitable but a minimal neuromuscular transmission remains. Under such circumstance, the number of twitches elicitable at 1 Hz after a 5-second tetanus is a quantitative indication of the neuromuscular transmission remaining. Double-burst stimulation, on the other hand, is especially useful when spontaneous recovery of neuromuscular transmission has progressed afar. When residual neuromuscular block becomes difficult to detect and train-of-four fade becomes difficult to ascertain, a double-burst stimulation (three stimuli 20 ms apart, recycled once in 3/4 sec) will elicit two "mini-tetani", the first of which much greater than the second. All electric impulses should be supramaximal.

Train-of-four stimulation plays a key role in the intraoperative management of neuromuscular block. When the neuromuscular tranmission is normal, the train of 4 twitches (0.5 sec between twitches) are equal and strong. With a minimal curariform block such as following "priming" or "defasciculation", the train-of-four will fade before the first twitch (t1) begins to diminish. With increased depression of neuromuscular transmission, the fourth (t4) and the first twitches will diminish parallelly. This continues until the t1 is depressed by about 75% and the t4 approaches zero. From this point on, the train-of-four ratio remains zero

as the t4, t3, t2 and t1 disappear in that order. The "train-of-four count" thus diminishes from 4, to 3, 2, 1, and then 0, as the t1 becomes depressed by approximately 75%, 85%, 90%, 95% and 100%. Beyond 100% depression of the t1, the neuromuscular transmission may be assessed by the post-tetanic count until even the post-tetanic twitches disappear. The range of neuromuscular block when the train-of-four count is 2, 3, or 4 provides very satisfactory relaxation in most patients during the surgical operations.

The train-of-four count is useful also at the end of surgery. Within the range of train-of-four count of 1, 2, 3 and 4, the residual neuromuscular block becomes more reversible as the train-of-four count increase. A train-of-four count of 1 or less usually means difficulty to reverse the block. A train-of-four count of 2 and 3 usually means success but has a significant risk of failure. A train-of-four count of 4 usually enables successful reversal of the neuromuscular block in a timely fashion with a usual dose of anticholinesterase.

It should be observed that during the onset of neuromuscular block the train-of-four fades less than during recovery, given the same depression of the t1. When t1 has just recovered its full amplitude (100%), the t4 is usually 0.75. A train-of-four ratio of 0.7 during spontaneous recovery usually signals adequate muscle power to permit removal of the trachea tube and spontaneous ventilation in an otherwise healthy subject.

III. Reversal of Neuromuscular Block

Pyridostigmine is advantageous over neostigmine in that it may produce less tachycardia and cross the blood-brain and the placental barriers less. However, neostigmine remains popular. Edrophonium produces less cardiovascular changes and acts more rapidly. A successful reversal of neuromuscular block occurs within 1-2 min of the administration of edrophonium. Incomplete reversal will manifest immediately. However, when the residual block is profound and protracted edrophonium may lack the required efficacy to complete and sustain a reversal. On balance, therefore, when the residual neuromuscular block is 75% or less (i.e. spontaneous recovery 25% or more and the train-of-four count equals 4), edrophonium 0.5 $mg \cdot kg^{-1}$ is the superior choice. This is particularly true when the neuromuscular blocker to be antagonized is not long-acting. With profound block, and especially if the relaxant is long-acting, neostigmine or pyridostigmine becomes a better choice. In general, when the train-of-four count is 2 or 3 and the relaxant to be antagonized is atracurium or vecuronium, edrophonium 0.5-1 $mg \cdot kg^{-1}$ and neostigmine 2.5 mg are approximately equally suitable.

Restoration of a train-of-four ratio to 0.7 or greater is adequate reversal for most patients postoperatively. At this train-of-four ratio the patient can sustain a headlift and adequate ventilation. Mivacurium, atracurium and vecuronium may need no reversal if adequate neuromuscular function can be documented. When in doubt, it is safer to administer the reversal agent. Long-acting nondepolarizing neuromuscular relaxants (pancuronium, pipecuronium, doxacuronium, metocurine, d-tubocurarine, gallamine) should be reversed as a routine.

IV. New and Old Neuromuscular Blocking Relaxants

Gallamine, decamethonium and metocurine are obsolete. D-tubocurarine is being replaced, and pancuronium is being challenged.

Neuromuscular relaxants in current use in the U.S.A. are:

Ultra-short-acting: succinylcholine

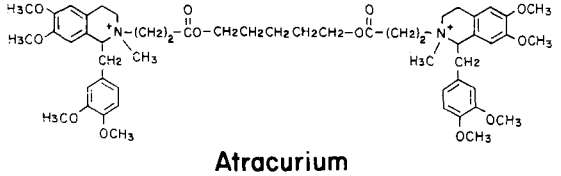
Short-acting: (pending)

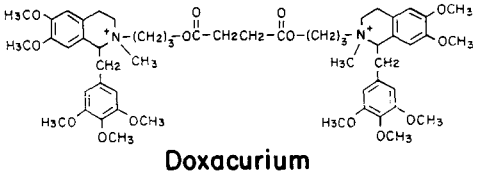
Intermediate duration: atracurium, vecuronium
Long-acting: pancuronium, pipecuronium, doxacurium
Ultra-long-acting: (none)

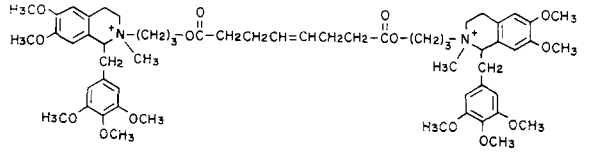
In addition, mivacurium[20,21] is an ester short-acting nondepolarizing relaxant currently pending approval by the Food and Drug Administration (FDA) for clinical use. Org. 9426,[22] Org. 9273,[23] and Org. 7268[24] are new steroidal neuromuscular relaxants of intermediate duration of action under various stages of development.

Succinylcholine has numerous complications and side effects.[6] Some complications are serious. Its use is being restricted to situations where rapid onset or very short duration of action is required, e.g. laryngospasm rapid-sequence intubation, electric shock therapy, reduction of dislocation, and setting of bone fracture. Besides, many more patients are being considered to have full stomach in recent anesthesia practice. These include pregnant woman, obese patients, patients with uremia, patients in labor and all those who recently ingested food or have esophageal dysfunctions. To reduce the chances of trachea aspiration of the gastric contents, rapid-sequence intubation is the technique of choice in these patients. Although "priming" was considered and acceptable alternative as a technique to secure the airway rapidly, succinylcholine remains the drug of choice for rapid paralysis. Therefore, succinylcholine will continue to be used until a nondepolarizing neuromuscular relaxant of rapid onset and short duration of action becomes clinically available.

Atracurium, mivacurium[20,21] and doxacurium[25] are esters of the same series (Fig. 3). Variation in the molecular structure results in different rates of hydrolysis by the plasma cholinesterase. One conspicuous example is that doxacurium has a succinic structure but is not hydrolyzed. The evolution from d-tubocurarine, stepwise, has reduced the potential for ganglion block and histamine release so that doxacurium has no side effects at all. Mivacurium is less histamine-releasing, shorter in duration of action, and possibly faster in onset than atracurium. Atracurium is less







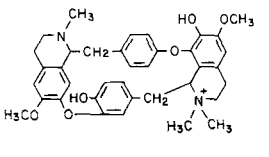


Fig. 3. Molecular structures of atracurium, mivacurium, doxacurium, and d-tubocurarine illustrating the structure-activity relationship of the benzyl isoquinolinium compounds.

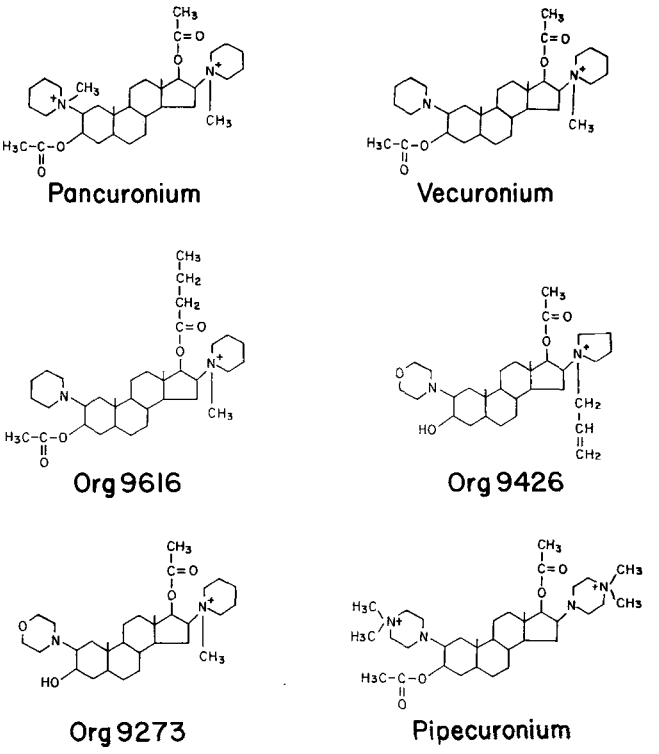


Fig. 4. Molecular structures of pancuronium, vecuronium, pipecuronium, and 3 experimental steroidal neuromuscular blocking relaxants undergoing various stages of clinical development.

histamine-releasing and has shorter duration of action than d-tubocurarine. Doxacurium is of approximately 2.5 times the duration and potency of d-tubocurarine. It does not produce tachycardia or release histamine. It is excreted unmetabolized by the kidneys. It is suitable for long surgical operations, especially when cardiovascular stability is of concern. These include cardiothoracic and neurosurgical operations. As predicted by mass law, it has slow onset.

Pancuronium, vecuronium, Org. 9426,[22] Org. 9273[23] and pipecuronium[26] are steroidal neuromuscular blocking agents. Pancuronium and pipecuronium are bisquaternary; the other three are monoquaternary (Fig. 4). The tachycardic effect of pancuronium is due to its acetylcholine-like structure on atom 3. Substitution in that position (pipecuronium) or rendering that nitrogen tertiary (vecuronium, Org. 9426, Org. 9273) eliminates the vagolytic effect. Pancuronium and pipecuronium are long-acting. Vecuronium has intermediate duration of action. Org. 9426 and Org. 9273 have intermediate duration of action, but they are somewhat shorter-acting and have faster onset of action than vecuronium. Both are in various stages of clinical evaluations in the U.S.A. Again, the more potent compounds have a slower onset than the less potent compounds in the series of analogs.

A nondepolarizing neuromuscular blocking relaxant of rapid onset and ultra-short duration of action with no side effects has been the goal of several groups of investigators for decades. Unfortunately, no such compounds will be available in the near future. A series of bisquaternary tropeinium compounds are being synthesized and evaluated for such purposes at Harbor-UCLA Medical Center.

Both atracurium and vecuronium have widespread acceptance in clinical

anesthesia. Between them, atracurium is somewhat advantageous in the predictability and consistency of recovery, while vecuronium is somewhat advantageous in the predictability and consistency of lack of side effects. Laudanosine is not a clinical issue. Histamine release sometimes occurs after atracurium, while bradycardia sometimes follows vecuronium especially in patients undergoing large-dose narcotic anesthesia. Serious anaphylactoid reactions are rare, but might occur following all neuromuscular relaxants. Those relaxants with histamine-releasing property are not particularly prone to cause anaphylactoid shock. With continuous use, vecuronium has a tendency to show cumulativeness. It also increased duration of action in the elderly and in hepatic failure.

V. Pharmacokinetics and Effects of Renal Failure or Hepatic Failure

Atracurium is unique in that it depends on neither plasma cholinesterase nor hepatic or renal functions for the termination of its neuromuscular effects. Hoffman elimination and hydrolysis by nonspecific esterases (not cholinesterases) account for its breakdown. It has the most cosistent duration of action under all clinical situations including old age, young age, and obesity. Theoretically, acidosis and hypothermia may prolong its duration of action. However, acidosis and hypothermia of the magnitude commonly encountered in the operating suite do not have clinically detectable influence on its breakdown. Gallamine, metocurine and decamethonium are solely dependent on the kidneys for excretion. The new long-acting relaxant doxacurium is also solely excreted by the kidneys, but its high specificity reduced the effects of renal failure on its duration of action. In renal failure, its duration of action is approximately doubled. Mivacurium is hydrolyzed by plasma cholinesterase and may be prolonged in the case of atypical plasma cholinesterase. The steroidal series of neuromuscular relaxants depend mainly on the liver for degradation and excretion. Their neuromuscular action may be prolonged by hepatic failure and to a lesser degree by renal failure.

VI. Drug Interaction

New information on drug interactions with the neuromuscular blocking relaxants points to a marked potentiation by desflurane.[27,28] Desflurane is a new halogenated volatile ether anesthetic currently being processed through the FDA in the U.S.A. It has the same molecular structure as isoflurane except for the substitution of the chlorine atom of isoflurane with a fluorine atom. It has a blood/gas solubility coefficient of 0.42, less than that of nitrous oxide. Its clinical profile is similar to isoflurane except that it is more volatile, less potent, and much faster in equilibration. Patients wake up faster and more smoothly. It is therefore particularly useful for outpatient surgery. Marked potentiation of neuromuscular relaxants by desflurane is an advantage.

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