Anesthesiology
V 44, No 4, Apr 1976

Medical Intelligence

Antagonism of Neuromuscular Blockade

*Ronald D. Miller, M.D.**

SINCE THE LAST REVIEW of the pharmacology and clinical use of muscle relaxants, in 1959,[1] almost half of the case reports in ANESTHESIOLOGY involving muscle relaxants have been concerned with problems with antagonism of neuromuscular blockade. Obviously, return of normal muscle function following relaxant administration is of prime importance to the restoration of adequate spontaneous ventilation. Because it is clinically important and previously has not been reviewed specifically, antagonism of neuromuscular blockade is discussed, following the outline below.

Evaluating Antagonism of a Nondepolarizing Blockade

CORRELATION BETWEEN TESTS OF NEUROMUSCULAR TRANSMISSION AND VENTILATION

Maintenance of adequate ventilation, particularly during stresses such as airway obstruction or vomiting, is of prime importance. Estimating the fraction of receptors occupied and detecting posttetanic facilitation or a sustained contraction in response to a tetanic stimulus are examples of tests used as indices of this function. There are few studies correlating tests of neuromuscular function with adequacy of ventilation, and the conclusions are often incomplete. Walts *et al.*[2] concluded that sustained muscular contraction in response to tetanic stimulation (30 Hz) for 5 seconds is a good test because it correlates with recovery to more than 90 per cent of vital capacity and maximum voluntary ventilation in human volunteers. They concluded that the head-raising test, the duration of which was not stated, is an unreliable index of recovery because it does not return to control when vital capacity and response to tetanic stimulation have recovered to 90 per cent of control. Perhaps the head-raising test is a more sensitive index of residual neuromuscular blockade. In fact, Johansen *et al.*[3] found head lift and hand grip strength to be 38 and 48 per cent of control when both inspiratory and expiratory flow rates were more than 90 per cent of control. Furthermore, Ali *et al.*[4] found inspiratory force to be only 70 per cent of control when vital capacity and expiratory flow rate were more than 90 per cent of control. Obviously, the most sensitive test stresses

OUTLINE

I. Evaluating Antagonism of a Nondepolarizing Blockade
  A. Correlation between tests of neuromuscular transmission and ventilation
  B. The use of receptor occlusion techniques to estimate the sensitivity of tests of neuromuscular function
  C. Clinical conclusions
II. Major Factors Influencing Antagonism of Neuromuscular Blockade—Acetylcholinesterase Inhibitors
III. Other Factors That May Influence Antagonism of Nondepolarizing Blockade
  A. Degree of recovery from neuromuscular blockade at which the acetylcholinesterase inhibitor is given
  B. Relaxant administered
  C. Acid–base balance
  D. Temperature
  E. Electrolyte imbalance
  F. Antibiotics
  G. Other drugs
IV. Antagonism of Desensitization Neuromuscular Blockade

* Associate Professor of Anesthesia and Pharmacology, Department of Anesthesia and Pharmacology, University of California Medical Center, 436 S, San Francisco, California 94143.

Accepted for publication November 17, 1975. Supported in Part by USPHS Research Grant 5P01 GM 15571-08.

Address reprint requests to Dr. Miller.

TABLE 1. Suggested Correlations Between Tests of Neuromuscular Transmission*

Peripheral Nerve Stimulation	Ventilation	Estimated Receptors Occupied (Per Cent)†
Reduced twitch height and sustained tetanus at 30 Hz‡	Normal tidal volume	75–80
Normal train-of-four	Normal expiratory flow rate and vital capacity	70–75
Sustained tetanus at 100 Hz‡	Normal inspiratory force	50
Sustained tetanus at 200 Hz‡	Normal head lift and hand grip test‡	33

* This table correlates data obtained from references 2–8.
† Estimated percentage of receptors that still could be occupied by a nondepolarizing muscle relaxant.
‡ Duration of tests 5 seconds.

the neuromuscular junction the most. Sensitivity depends on both the intensity and the duration of the stress applied. For example, a tetanic stimulus of 30 Hz for 10 seconds may be more stressful than one of 100 Hz for 1 second. Making several assumptions, I organized data from several studies[2–8] to correlate tests of ventilation and neuromuscular function with estimated receptor occupancy (table 1). Even when the result is normal, none of these tests assures that all of the receptors are free of relaxant. The data suggest that the sensitivities of the tests in detecting residual block are: head lift > hand grip > inspiratory force > inspiratory and expiratory flow rates > sustained contraction in response to a tetanic stimulus (30 Hz) and normal vital capacity > normal tidal volume and normal twitch height (table I). This sensitivity scale assumes that applications of these tests in all studies are identical. This probably is not true. For example, Johansen *et al.*[2] did not state the durations of head lift and hand grip tests. I assumed that the common time of 5 seconds was used.

Ali *et al.* proposed "train-of-four" stimulation as the test of choice. Four supramaximal stimuli at 2 Hz are delivered to the ulnar nerve,[3] and the ratio of the amplitude of the fourth twitch to the amplitude of the first twitch is used as an index of nondepolarizing neuromuscular blockade. The test does not require a control (pre-relaxant) twitch and is not painful. However, 70 per cent of the receptors can be occupied and still permit a normal "train-of-four."[6] Thus, the test is slightly more sensitive than that using a single twitch and tetanic stimuli at 30 Hz (table 1).

THE USE OF RECEPTOR OCCLUSION TECHNIQUES TO ESTIMATE THE SENSITIVITY OF TESTS OF NEUROMUSCULAR FUNCTION

The ability to sustain contraction in response to a high-frequency tetanic stimulus (100 Hz or more) is probably the most sensitive clinical index of antagonism of neuromuscular blockade.[8] Using receptor occlusion techniques in experimental animals, Waud and Waud compared the fractions of receptors that must be not blocked by relaxant in order for the results of tests of neuromuscular function to be normal.[5] The technique estimates the fraction of receptors blocked by a nondepolarizing relaxant by determining a dose–response depolarization curve from various doses of agonist (succinylcholine) in the absence and presence of the blocker (*d*-tubocurarine, gallamine). The fraction of receptors not blocked by the nondepolarizing relaxant and therefore still available for neuromuscular transmission can be estimated from the dose ratio of the agonist and blocker. For example, in the presence of *d*-tubocurarine, intra-arterial injection of 30 nmoles of succinylcholine might be necessary to produce the same depolarization produced by 10 nmoles in the absence of *d*-tubocurarine. The analytical expression for fractional receptor occlusion is (dose ratio − 1)/dose ratio or, in the above case, ⅔. We would then conclude that 66 per cent of the receptors are blocked by *d*-tubocurarine. The accuracy of this technique is based on the assumption that succinylcholine is a pure agonist of depolarization and that desensitization of the

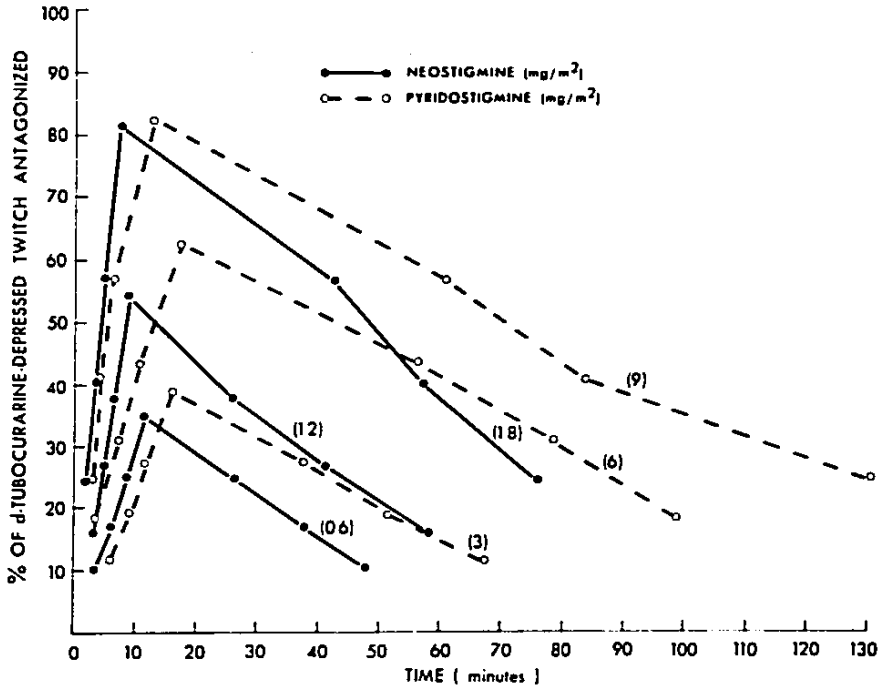

FIG. 1. Plot of time and percentage of the *d*Tc-depressed twitch antagonized. The twitch was depressed to 10 per cent of the control height by a constant infusion of *d*Tc. Each dot represents the mean for five patients (with permission of author and ANESTHESIOLOGY[16]).

endplate does not occur during the study. Waud and Waud separated administrations of succinylcholine by one hour to minimize the possibility of desensitization.[4] Preliminary studies in man indicate that the above-mentioned results in animals can be extrapolated to man.[7] All other tests used to measure neuromuscular function allow a normal response with a significant number of receptors still blocked, even with a tetanic stimulus of 200 Hz (table 1). These results suggest that no clinical test to determine whether all receptors are free of a relaxant is available.

CLINICAL CONCLUSIONS

In spite of the above considerations, we do not know what proportion of receptors must be available or how sensitive a test must be to insure adequate muscle strength to overcome airway obstruction and to permit coughing effectively. How much acetylcholinesterase inhibitor should be given? Several authors recommend titrating the amount of acetylcholinesterase inhibitor to a specific end point. Most frequently suggested is a sustained contraction in response to a tetanic stimulus of 30–50 Hz.[5,8–10] However, this and other tests may not detect subtle degrees of neuromuscular blockade. In practice, I administer slightly more neostigmine or pyridostigmine than necessary to effect a sustained contraction in response to a tetanic stimulus of 30–50 Hz. For example, if 2.5 mg neostigmine were sufficient to restore twitch height to control levels and sustain tetanus at 50 Hz, I would administer 3.0 mg neostigmine in an effort to insure the availability of additional receptors needed to overcome airway obstruction.

Major Factors Influencing Antagonism of Neuromuscular Blockade—Acetylcholinesterase Inhibitors

Termination of a nondepolarizing neuromuscular blockade is accomplished by increasing the acetylcholine concentration at the postjunctional membrane and/or by allowing elimination (and time) to decrease plasma relaxant concentration. An acetylcholinesterase inhibitor (neostigmine, pyridostigmine) allows acetylcholine to accu-

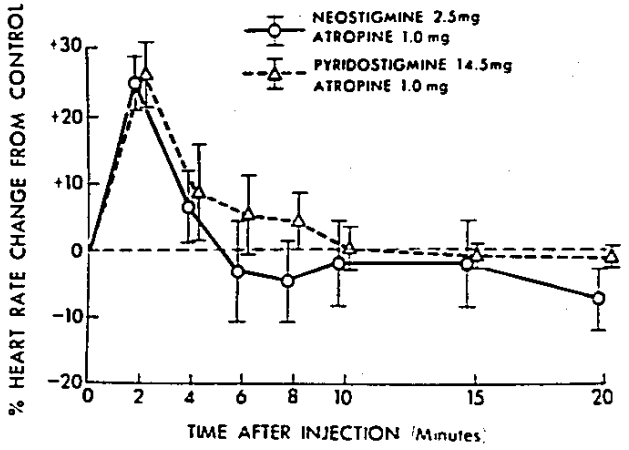

FIG. 2. Heart rate changes during antagonism of *d*Tc-induced neuromuscular blockade by neostigmine (n = 5 patients) and pyridostigmine (n = 5 patients) with atropine, 1.0 mg (with permission of author and ANESTHESIOLOGY[12]).

mulate at the neuromuscular junction. Nondepolarizing relaxants and acetylcholine alter neuromuscular transmission in a competitive manner. Even though a nondepolarizing relaxant increases the amount of acetylcholine necessary to achieve muscle contraction, maximum contraction can occur with a sufficiently large dose of acetylcholine. These observations suggest that *d*Tc competes with acetylcholine for endplate receptors; however, Waser,[11] as a result of a study using autoradiography, has suggested that acetylcholine and *d*Tc act on different receptors. Although the physical nature of these receptors remains obscure, the presumed acetylcholine receptor sites (identified by binding of ^{14}C-muscarone) have been distinguished from the *d*Tc receptors (identified by binding of ^{14}C-curarine). Labeled acetylcholine was not used to identify acetylcholine receptors because it is hydrolyzed too rapidly for adequate observation (muscarone is a stable acetylcholine preparation). From these observations, Waser[11] postulated that *d*TC may obstruct pores through which ionic flux necessary for depolarization travels. Acetylcholine may act on sites that surround these pores, perhaps indirectly causing a conformational change that reduces the affinity of relaxant for the pore. Whether the same or different are receptors are involved, acetylcholine–*d*Tc interaction fits the definition of a competitive interaction.

Trial-and-error demonstrates that 2 to 3 mg neostigmine will antagonize most nondepolarizing blocks in the average adult patient.[9,10] Normally, the duration of action of neostig-

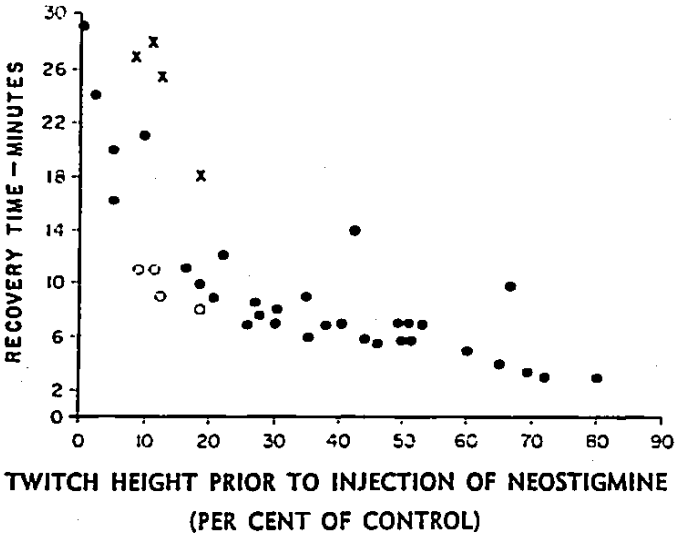

FIG. 3. Time from injection of 2.5 mg neostigmine to return of control twitch height in attempts to antagonize a pancuronium-induced neuromuscular blockade. The "X" and "O" represent four patients who received pancuronium on two occasions each, with the injections of neostigmine made at the same stages of recovery. See original article for a more detailed discussion (with permission of author and ANESTHESIOLOGY[9]).

mine equals or exceeds those of the relaxants, so paralysis does not reappear at the termination of neostigmine action. If the rate of relaxant elimination is decreased, as with renal failure, the relaxant concentration may be high enough for paralysis to reappear after the neostigmine effect has dissipated.[12]

Edrophonium, galanthamine, neostigmine, and pyridostigmine are acetylcholinesterase inhibitors that antagonize nondepolarizing blockade. Germine diacetate and germine-3-acetate, which are veratrum alkaloids, antagonize the neuromuscular blocks from both nondepolarizing and depolarizing neuromuscular blockers[13] without undesired muscarinic side effects. Unlike the other antagonists, germine agents do not inhibit acetylcholinesterase, nor do they affect acetylcholine release or motor endplate function.[14] When antagonizing *d*Tc and succinylcholine, germine acetate must affect the nerve or muscle.[14] Germine acetate, germine diacetate, and galanthamine (an acetylcholinesterase inhibitor) are not available in the United States.

The duration of action of edrophonium is too short for it to be a useful antagonist of nondepolarizing blockade. The durations of action of neostigmine and pyridostigmine are sufficient to be clinically useful. Preliminary studies suggested that pyridostigmine might be preferable to neostigmine because of a longer duration of action and fewer muscarinic side effects.[15] Subsequent studies in man confirm that pyridostigmine has a duration of action approximately 40 per cent longer than that of neostigmine when equivalent antagonistic doses are used (fig. 1).[16] Although pyridostigmine has a longer duration of action, its time to onset is 5 to 7 minutes longer (fig. 1). Fogdall and Miller found no difference between the cardiac muscarinic effects of neostigmine and pyridostigmine (fig. 2).[17] Although many clinicians advise establishing a vagolytic effect from atropine before administering neostigmine, this is unnecessary, since the vagolytic effects precede the cardiac muscarinic effects of neostigmine by 1 to 2 minutes (fig. 2). I administer neostigmine or pyridostigmine and atropine concomitantly. Other muscarinic effects of neostigmine and pyridostigmine have not been studied comparatively. Other than a slightly longer duration of action, pyridostigmine appears to offer no advantage over neostigmine.

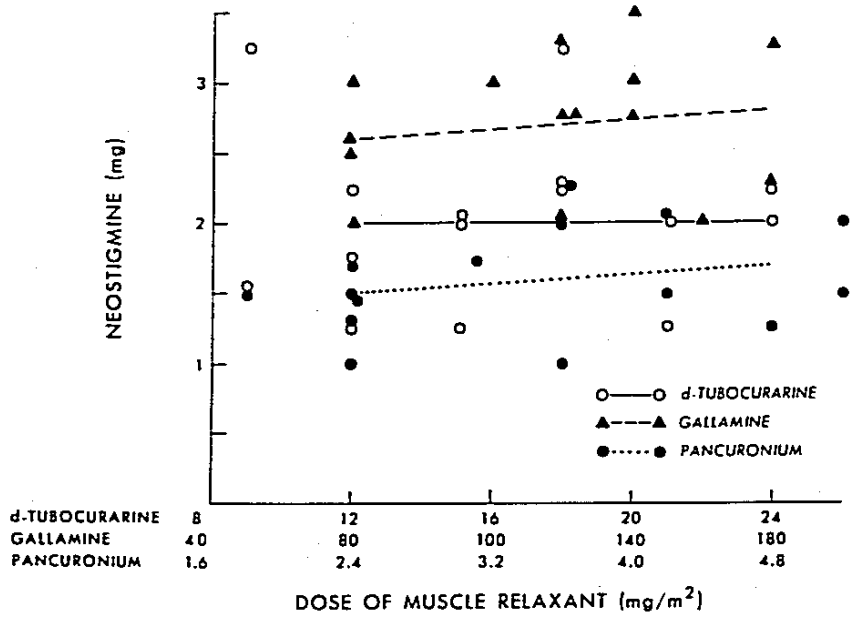

FIG. 4. Correlation between doses of relaxants and doses of neostigmine needed for tetanus to be sustained at 50 Hz. The lines represent analysis of linear regression (with permission of author and ANESTHESIOLOGY[19]).

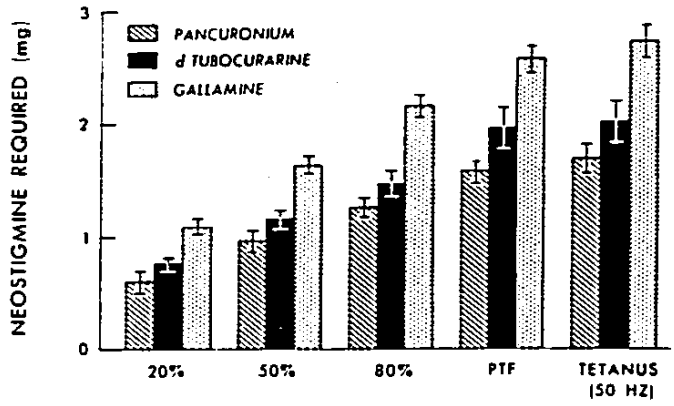

FIG. 5. Doses of neostigmine needed for 20, 50, and 80 per cent recovery of control twitch height, absence of posttetanic facilitation (PTF), and sustained tetanus (n = 5) (mean ± SE) (with permission of author and ANESTHESIOLOGY[10]).

Other Factors That May Influence Antagonism of Nondepolarizing Blockade

DEGREE OF RECOVERY FROM NEUROMUSCULAR BLOCKADE AT WHICH THE ACETYLCHOLINESTERASE INHIBITOR IS GIVEN

The degree of neuromuscular blockade at the time when neostigmine is administered determines the speed and extent of antagonistic action by neostigmine. When twitch height is more than 20 per cent of control, time from neostigmine administration (2.5 mg) to attainment of control twitch height is 3–14 minutes. With twitch heights less than 20 per cent of control, recovery takes 8–29 minutes (fig. 3).[9] When twitch height is 5 per cent of the control, the dose of neostigmine necessary to antagonize *d*-tubocurarine-, gallamine-, or pancuronium-induced neuromuscular blockade is not dependent on the dose of relaxant administered (fig. 4).[10] Thus, the degree of recovery from a neuromuscular block at which reversal is initiated will determine the speed of recovery, and appears to be a far more important determinant of neostigmine requirement than the dose of relaxant administered. This is true if the same fraction of receptors is occupied with relaxant when the twitch has returned to a given percentage of control twitch height regardless of the dose of relaxant administered.

RELAXANT ADMINISTERED

The neuromuscular blockade from gallamine requires more neostigmine for antagonism than that from *d*Tc or pancuronium (fig. 5).[10] Monks[18] found that neostigmine-induced recovery from a *d*Tc- or pancuronium-induced block was faster than recovery from a gallamine-induced block. He concluded that blockade by *d*Tc or pancuronium is "more easily reversed" than gallamine-induced block. Although these studies imply that gallamine, with which more neostigmine is needed for antagonism, is less desirable, all the gallamine-induced blocks in Miller's study[10] were completely antagonized by neostigmine. Monks[18] did not follow the twitch response until complete recovery occurred. Does the fact that gallamine requires more neostigmine for antagonism represent an undesirable clinical effect? Since in both studies all neuromuscular blocks were antagonized successfully, the need to administer 0.5 to 1.0 mg more neostigmine does not pose a significant problem.

ACID–BASE BALANCE

Respiratory acidosis augments a *d*Tc-induced block and limits and opposes its antagonism by neostigmine (fig. 6).[19–21] If a patient hypoventilates in the recovery room, attempts to antagonize a residual *d*Tc-induced block may fail. Administration of narcotics to relieve pain may increase the likelihood of this untoward event. Such a sequence results in a positive feedback where respiratory depression produces more acidosis and relaxant effect and hence, more respiratory depression.

Although clinical observations suggest that

both respiratory and metabolic acidosis interfere with neostigmine antagonism of *d*-tubocurarine, this has not been substantiated.[22] In fact, Miller *et al.* found that metabolic alkalosis, but not metabolic acidosis, limited neostigmine antagonism of *d*Tc (fig. 7).[21] These results suggest that extracellular *p*H *per se* may not be as important as changes in electrolytes and intracellular *p*H. For example, serum potassium and calcium levels decrease when metabolic alkalosis is induced. Would metabolic alkalosis interfere with neostigmine antagonism of *d*Tc if these electrolytes were maintained within normal limits? Could acutely induced metabolic alkalosis produce greater changes in transmembrane potentials than that which is chronically induced? These possibilities suggest that looking at extracellular *p*H alone is insufficient to predict the effects of acid–base changes on neostigmine antagonism of *d*Tc.

The effect of acid–base balance on neostigmine antagonism of pancuronium has not been explored. Findings from *d*Tc–neostigmine interaction may not apply to a pancuronium–neostigmine interaction. For example, unlike *d*Tc-induced blockade, pancuronium-induced blockade is apparently not affected by changes in ventilation.[23]

Temperature

It is a common belief that neostigmine-antagonized *d*-tubocurarine-induced neuromuscular blockade during hypothermia may reappear upon rewarming. However, McKlveen *et al.*[24] were unable to confirm this assumption in a study of dogs. They partially antagonized a *d*Tc-induced block with neostigmine at 32 C. When the muscle was warmed rapidly to normothermia, blockade did not reappear.[24] These results challenge the conclusions of other studies that state that a *d*Tc-induced block is diminished by hypothermia.[25,26] In fact, hypothermia recently was found to diminish *d*Tc-induced blockade only transiently; then, blockade was enhanced[27]; the latter has been confirmed by Foldes *et al.*†

† Foldes FF, Kuze S, Erdmann KA: The influence of temperature on the activity of neuromuscular blocking agents, Abstracts of Scientific Papers, 1974 Annual Meeting of the American Society of Anesthesiologists, pp 125–126.

Perhaps the effects of hypothermia on *d*Tc uptake and elimination explain some of the differences of opinion. Results obtained *in vitro* would not be affected by uptake and distribution. Some investigators found less neuromuscular blockade by *d*Tc in a cool limb compared with a warm limb.[26] I propose that these results follow from the lesser blood flow to the cool limb, which allows a greater fraction of the *d*Tc to reach the warm limb. Thus, our conclusion, based on cat studies *in vivo*, of greater *d*-tubocurarine potency during hypothermia probably relates more to relaxant elimination than to a direct effect at the myoneural junction.[28] Hypothermia reduces renal and biliary excretion, which are the routes of excretion for *d*-tubocurarine. For example, 43 per cent less *d*-tubocurarine is necessary to maintain a given plasma level of *d*-tubocurarine at a temperature of 28 C.[28] Combining all the effects on the neuromuscular junction and on uptake and distribution, I have concluded that less *d*Tc is necessary for neuromuscular blockade during hypothermia.

Hypothermia *per se* does not alter the ability or amount of neostigmine needed to antagonize *d*-tubocurarine-induced blockade.[28] When an excess of *d*-tubocurarine is given because it is thought that more is needed during hypothermia, perhaps a neuromuscular blockade too intense for neostigmine to antagonize may be induced.

Electrolyte Imbalance

Although electrolyte imbalance has been the subject of several reviews,[29,30] few data on the effects of electrolyte imbalance on nondepolarizing neuromuscular blockade and its antagonism by neostigmine are available. The lack of studies of the effects of electrolyte imbalance and dehydration on actions of neuromuscular blockers and their antagonists makes the following opinions speculative only. Low extracellular concentrations of potassium supposedly enhance the blocks from nondepolarizing relaxants and diminish the ability of neostigmine to antagonize the blocks.[29,30] This opinion is based on the increase in the endplate transmembrane potential that results from a higher ratio of intracellular to extracellular potassium levels (sodium levels are of relatively little importance).[31] Thus, a decrease in extracellular

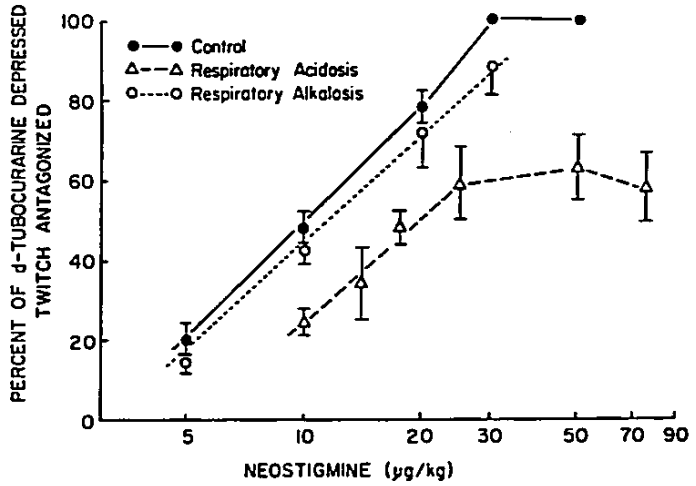

FIG. 6. Correlation between dose of neostigmine and percentage of *d*Tc-depressed twitch antagonized in cats. During respiratory alkalosis the Pa_{CO_2} and *p*H were 17.4 torr and 7.53, and during respiratory acidosis, 66.1 torr and 7.13 (with permission of author and ANESTHESIOLOGY[21]).

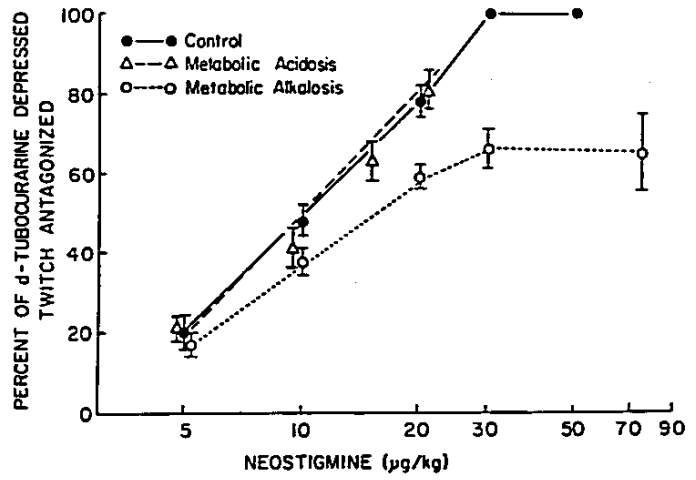

FIG. 7. Correlation between dose of neostigmine and percentage of *d*Tc-depressed twitch antagonized in cats. During metabolic alkalosis the Pa_{CO_2} and *p*H were 36.3 torr and 7.59, and during metabolic acidosis, 37.7 torr and 7.01 (with permission of author and ANESTHESIOLOGY[21]).

potassium causes hyperpolarization and increases resistance to depolarization. However, the endplate is only one part of the contractile mechanism, the remainder of which may be affected in a contrary fashion. For example, a low extracellular potassium level also should increase the transmembrane potential of the motor nerve terminal. Although the threshold for depolarization is increased once depolarization occurs, the nerve action potential will be larger, and this should augment acetylcholine release and postjunctional depolarization. I do not know which of the opposing pre- and postjunctional changes from hypokalemia is dominant.

Cohen[30] and Feldman[29] speculate that in chronic diseases, both intra- and extracellular potassium decrease without affecting transmembrane potential. Therefore, the responses to muscle relaxants and their antagonists should be normal. Skeletal muscle transmembrane potassium ratios are not altered in severely ill patients[32]; however, their muscle transmembrane potentials are decreased because of increased intracellular sodium levels. Cunningham *et al.*[32] speculate that this results from a defect in sodium transport, which is common in seriously ill patients. Although, relatively, sodium is not as important as potassium, this decreased potential actually should antagonize *d*-tubocurarine. Yet concomitant dehydration in seriously ill patients should concentrate *d*-tubocurarine present in plasma, thereby increasing relaxant activity. Obviously, studies of dehydrated patients who have electrolyte imbalances

TABLE 2. Interaction of Antibiotics, Muscle Relaxants, Neostigmine, and Calcium

Antibiotic	Neuromuscular Block from Antibiotic Alone Antagonized by		Increase in Neuromuscular Block of		Neuromuscular Block from Antibiotic–*d*Tc Antagonized by	
	Neostigmine	Calcium	*d*Tc	SCh	Neostigmine	Calcium
Neomycin	Sometimes	Sometimes	Yes	Yes	Usually	Usually
Streptomycin	Sometimes	Sometimes	Yes	Yes	Yes	Usually
Gentamycin	Sometimes	Yes	Yes	*	Sometimes	Yes
Kanamycin	Sometimes	Sometimes	Yes	Yes	Sometimes	Sometimes
Paromomycin	Yes	Yes	Yes	*	Yes	Yes
Viomycin	Yes	Yes	Yes	*	Yes	Yes
Polymyxin A	No	No	Yes	*	No	No
Polymyxin B	No†	No	Yes	Yes	No†	No
Colistin	No	Sometimes	Yes	Yes	No	Sometimes
Tetracycline	No	*	Yes	No	Partially	Partially
Lincomycin	Partially	Partially	Yes	*	Partially	Partially
Clindamycin	Partially	Partially	Yes	*	Partially	Partially

* Not studied.
† Block augmented by neostigmine.

are needed to clarify these confusing and often opposing opinions.

The effects of magnesium- and calcium-induced alterations of neuromuscular blockade have been studied in animals and in man. Magnesium sulfate, given for treatment of pre-eclampsia and eclamptic toxemia, enhances the neuromuscular blocking properties of both *d*-tubocurarine and succinylcholine.[33,34] Magnesium decreases 1) the amount of acetylcholine released from the motor nerve terminal, 2) the depolarizing action of acetylcholine on the postjunctional membrane and the excitability of the muscle fiber itself, and 3) the amplitude of the end-plate potential.[35] Thus, magnesium enhances *d*-tubocurarine-induced blockade by reducing acetylcholine output from the motor nerve terminal and by reducing sensitivity of the postjunctional membrane. I cannot explain why the action of succinylcholine is enhanced unless a desensitization block rapidly occurs with high plasma magnesium levels.

Although calcium enhances the release of acetylcholine from the motor nerve terminal and enhances excitation–contraction coupling in muscle,[36] it also stabilizes the postjunctional membrane. This stabilization may explain why calcium only partially antagonizes magnesium-*d*-tubocurarine-induced blockade.[34] Calcium is less effective in antagonizing magnesium-succinylcholine-induced blockade, and will augment a desensitization block from succinylcholine. Again, this is probably explained by membrane stabilization.[37] A prolonged block should be anticipated when a magnesium-relaxant combination is used, since neostigming and calcium are only partially effective antagonists.

ANTIBIOTICS

More than 120 reports concerning enhancement of neuromuscular blockade from muscle relaxants by antibiotics have appeared in the literature.[38] Although most antibiotics produce neuromuscular blockade similar to that produced by *d*-tubocurarine (*i.e.*, fade in muscle strength in response to tetanic stimulation and posttetanic facilitation), these blocks are antagonized inconsistently by neostigmine (table 2). Corrado[39] suggests that streptomycin, neomycin, and kanamycin chelate calcium and produce neuromuscular blockade by reducing serum calcium concentrations. However, ionized calcium levels were not measured. Several reports of relaxant–antibiotic-induced blockades successfully antagonized by calcium followed this suggestion.[40]

Pittinger found no decrease in ionized calcium levels with streptomycin.[41] Other reports support antibiotic-induced hypocalcemia (both total and ionized) as a mechanism of neuromuscular blockade. Adams and Mathew suggest that neomycin inhibits binding and retention of calcium at an unknown prejunctional membrane site.[42] This calcium is essential for release of quanta of acetylcholine.[43] If so, why is calcium an incomplete

antagonist?[44,45] If acetylcholine release is only partially inhibited, why is neostigmine an inconsistent antagonist? The failure of neostigmine to antagonize such a block completely also contradicts a competitive mechanism of action similar to that of *d*Tc. Using microelectrode techniques, Dretchen *et al.* found that streptomycin at low doses stimulates the motor nerve terminal and at higher doses inhibits motor nerve terminal function and reduces the sensitivity of the endplate to acetylcholine.[46] The dose dependence of different mechanisms of action may explain why neostigmine will antagonize a partial but not a complete block from neomycin.[45]

The search for a common mechanism of antibiotic-induced neuromuscular blockade probably is futile because of several possible mechanisms inherent in the variety of antibiotics that can cause blockade. In other words, the mechanisms of neuromuscular blockade are probably different for the various antibiotics, which may account for some of the conflicting suggestions for effective remedies in the case reports (table 2). I arbitrarily administer neostigmine to 5 mg/70 kg; more neostigmine may augment the block.[48,49]‡ When this is ineffective, calcium chloride, 1 g/70 kg in divided doses, should be given. If these measures fail, then controlled ventilation until the neuromuscular blockade terminates spontaneously is indicated.

Other Drugs

In small doses, most local anesthetics enhance the neuromuscular blockades resulting from both nondepolarizing and depolarizing muscle relaxants.[50,51] For example, Telivuo[50] observed additional decreases in twitch height and tidal volume from lidocaine, mepivacaine, prilocaine, and bupivacaine in patients partially paralyzed with nortoxiferine. Local anesthetics depress posttetanic potentiation; have a prejunctional action; stabilize both the postjunctional and muscle membranes, as evidenced by inhibition of acetylcholine-induced muscular contractions; and displace calcium from the sarcolemma.[52] Also, procaine inhibits plasma cholinesterase and may augment neuromuscular blockade by succinylcholine. In addition to local anesthetics, antiarrhythmic drugs such as quinidine, propranolol, and diphenylhydantoin augment nondepolarizing neuromuscular blockade.[53,54] The ability of acetylcholinesterase inhibitors to antagonize a mixed local anesthetic—or antiarrhythmic—nondepolarizing blockade has not been studied adequately. Preliminary studies suggest neostigmine may be ineffective as an antagonist. For example, edrophonium is ineffective in antagonizing a nondepolarizing blockade after quinidine.[54]

Ketamine enhances *d*-tubocurarine-induced neuromuscular blockade by depressing the sensitivity of the postjunctional membrane to acetylcholine.[55,56] The ability of neostigmine to antagonize ketamine-augmented neuromuscular blockade has not been studied. In large, non-clinical, doses, sedative–hypnotics and barbiturates augment *d*Tc-induced blockade. These interactions probably are not clinically important.[52,57] Although many other drugs have neuromuscular effects, few data have been added since the review of Foldes.[1]

Antagonism of Desensitization Neuromuscular Blockade

Gissen *et al.* found that neostigmine antagonizes desensitization blockade only in the absence of succinylcholine in arterial blood.[58] Although explanations for desensitization blockade by succinylcholine are numerous and controversial,[59,60] I believe certain observations indicate neostigmine will antagonize blockade by succinylcholine regardless of the mechanism. Gissen *et al.* concluded that without a method to determine the concentration of succinylcholine in blood, attempts to antagonize desensitization blockade by succinylcholine with acetylcholinesterase inhibitors should be avoided.[61] In contrast, my experience with more than 25 patients who each received 300–1,200 mg succinylcholine (Becker *et al.*, unpublished data), and numerous other case reports,[61] suggest that neostigmine is a reliable antagonist of a desensitization block. Administration of neostigmine or pyridostigmine is indicated if the following criteria are met: 1) some respiratory

‡ Becker L, Miller RD: Clindamycin enhances a nondepolarizing neuromuscular blockade, Abstracts of Scientific Papers, 1975 Annual Meeting of the American Society of Anesthesiologists, pp 203–204.

activity should be present (*i.e.*, neostigmine should not be given when the patient is apneic); 2) desensitization block should be present, as indicated by an unsustained contraction in response to a tetanic stimulus of 30–50 Hz and posttetanic facilitation; 3) there should be an increase in the strength of the response to edrophonium, a short-acting acetylcholinesterase inhibitor.

Summary

Although acetylcholinesterase inhibitors are accepted antagonists of nondepolarizing neuromuscular blockade, many basic questions are still unanswered. What is the relationship between receptor occupancy and adequate ventilation? What are the effects of changes in acid–base balance and temperature? What are the mechanisms of the various antibiotic-induced neuromuscular blockades, and what antagonizes them? This review is an attempt to summarize the known factors influencing relaxant blocks and to identify the unknown factors. The need for further studies is obvious.

The author thanks Edmond I. Eger, II, M.D., Lawrence Becker, M.D., and Ms. Trudy Garrettson for their help in the preparation of this manuscript.

References

1. Foldes FF: Factors which alter the effects of muscle relaxants. ANESTHESIOLOGY 20:464–504, 1959
2. Walts LF, Levin N, Dillon JB: Assessment of recovery from curare. JAMA 213:1894–1896, 1970
3. Johansen SH, Jorgensen M, Molbech S: Effect of tubocurarine on respiratory and non-respiratory muscle power in man. J Appl Physiol 19:990–994, 1964
4. Ali HH, Wilson RS, Savarese JJ: The effect of tubocurarine on indirectly elicited train-of-four muscle response and respiratory measurements in humans. Br J Anaesth 47:570–573, 1975
5. Waud BE, Waud DR: The relation between tetanic fade and receptor occlusion in the presence of competitive neuromuscular block. ANESTHESIOLOGY 35:456–464, 1971
6. Waud BE, Waud DR: The relation between the response to "train-of-four" stimulation and receptor occlusion during competitive neuromuscular block. ANESTHESIOLOGY 37:413–416, 1972
7. Yamamura Y: Safety margin of neuromuscular transmission in man. Jap J Anesth 22:1457–1462, 1973
8. Gissen AJ, Katz RL: Twitch, tetanus, and post-tetanic potentiation as indices of nerve–muscle block in man. ANESTHESIOLOGY 30: 481–487, 1969
9. Katz RL: Clinical neuromuscular pharmacology of pancuronium. ANESTHESIOLOGY 34:550–556, 1971
10. Miller RD, Larson CP Jr, Way WL: Comparative antagonism of *d*-tubocurarine-, gallamine-, and pancuronium-induced neuromuscular blockades by neostigmine. ANESTHESIOLOGY 37:503–509, 1972
11. Waser PG: Receptor localization by autoradiographic techniques. Ann NY Acad Sci 144: 737–755, 1967
12. Miller RD, Cullen DJ: Renal failure and post-operative respiratory failure: Recurarization? Br J Anaesth 48: (March) 1976
13. Flacke W, Katz RL, Flacke JW, et al: Germine diacetate as an antagonist of depolarizing and nondepolarizing neuromuscular blocking agents in man (abstr). ANESTHESIOLOGY 29:850–854, 1968
14. Detwiler PB: The effects of germine-3-acetate on neuromuscular transmission. J Pharmacol Exp Ther 180:244–254, 1972
15. Katz RL: Pyridostigmin (Mestinon) as an antagonist of *d*-tubocurarine. ANESTHESIOLOGY 28:528–534, 1967
16. Miller RD, Van Nyhuis LS, Eger EI II, et al: Comparative times to peak effect and durations of action of neostigmine and pyridostigmine. ANESTHESIOLOGY 41:27–33, 1974
17. Fogdall RP, Miller RD: Antagonism of *d*-tubocurarine- and pancuronium-induced neuromuscular blockades by pyridostigmine in man. ANESTHESIOLOGY 39:504–509, 1973
18. Monks S: The reversal of non-depolarizing relaxants. Anesthesia 27:313–318, 1972
19. Hughes R: The influence of changes in acid–base balance on neuromuscular blockade in cats. Br J Anaesth 42:658–668, 1970
20. Katz RL, Wolf CE: Neuromuscular and electromyographic studies in man: Effects of hyperventilation, carbon dioxide inhalation and *d*-tubocurarine. ANESTHESIOLOGY 25:781–787, 1964
21. Miller RD, Van Nyhuis LS, Eger EI II, et al: The effect of acid–base balance on neostigmine antagonism of *d*-tubocurarine-induced neuromuscular blockade. ANESTHESIOLOGY 42:377–383, 1975
22. Bush GH, Baraka A: Factors affecting the termination of curarization in the human subject. Br J Anaesth 36:356–362, 1964
23. Dann WL: The effects of different levels of ventilation on the action of pancuronium in man. Br J Anaesth 43:959–962, 1971
24. McKlveen JF, Sokoll MD, Gergis SD, et al: Absence of recurarization upon rewarming. ANESTHESIOLOGY 38:153–156, 1973
25. Bigland B, Goetzee B, Maclagan J, et al: The effect of lowered muscle temperature on the action of neuromuscular blocking drugs. J Physiol 141:425–434, 1958
26. Zaimis E, Cannard TH, Price HL: Effects of lowered muscle temperature upon neuro-

muscular blockade in man. Science 128:34–35, 1958
27. Zink J, Bose D: Cold potentiation of neuromuscular transmission in the avian biventer cervicis muscle. Eur J Pharmacol 28:149–156, 1974
28. Miller RD, Van Nyhuis LS, Eger EI II: The effect of temperature on a *d*-tubocurarine neuromuscular blockade and its antagonism by neostigmine. J Pharmacol Exp Ther 195:237–242, 1975
29. Feldman SA: Effect of changes in electrolytes, hydration, and *p*H upon the reactions to muscle relaxants. Br J Anaesth 35:546–551, 1963
30. Cohen EN: Patients with altered sensitivity. Clin Anesth 2:76–93, 1966
31. Feldman SA: Neuromuscular transmission, Muscle Relaxants. London, W. B. Saunders, 1973, pp 11–29
32. Cunningham JN Jr, Carter NW, Rector FC Jr, et al: Resting transmembrane potential difference of skeletal muscle in normal subjects and severely ill patients. J Clin Invest 50:49–59, 1971
33. Giesecke AH, Morris RE, Dalton MD, et al: Of magnesium, muscle relaxants, toxemic parturients, and cats. Anesth Analg (Cleve) 47:689–695, 1968
34. Ghoneim MM, Long JP: The interaction between magnesium and other neuromuscular blocking agents. ANESTHESIOLOGY 32:23–27, 1970
35. del Castillo J, Engbaek L: The nature of the neuromuscular block produced by magnesium. J Physiol 124:370–384, 1954
36. Manthey AA: The effect of calcium on the desensitization of membrane receptors at the neuromuscular junction. J Gen Physiol 49: 963–976, 1966
37. Badola RP, Chatterji S, Pandey K, et al: Effects of calcium on neuromuscular block by suxamethonium in dogs. Br J Anaesth 43: 1027–1035, 1971
38. Pittinger CB, Eryasa Y, Adamson R: Antibiotic-induced paralysis. Anesth Analg (Cleve) 49:487–501, 1970
39. Corrado AP: Respiratory depression due to antibiotics: Calcium in treatment. Anesth Analg (Cleve) 42:1–5, 1963
40. Zauder HL, Barton N, Bennett EJ, et al: Colistimethate as a cause of postoperative apnea. Canad Anaesth Soc J 13:607–610, 1966
41. Pittinger C, Adamson R: Antibiotic blockade of neuromuscular function. Annu Rev Pharmacol 21:169–184, 1972
42. Adams HR, Mathew BP: The cumulative neuromuscular blocking effect of neomycin. Arch Int Pharmacodyn 210:288–298, 1974
43. Dodge FA Jr, Rahamimoff R: Cooperative action of calcium ions in transmitter release at the neuromuscular junction. J Physiol (Lond) 193:419–432, 1967
44. Fisk GC: Respiratory paralysis after a large dose of streptomycin. Report of a case. Br Med J 1:556–557, 1961
45. Stanley VF, Giesecke AH Jr, Jenkins MT: Neomycin–curare neuromuscular block and reversal in cats. ANESTHESIOLOGY 31:228–232, 1969
46. Dretchen KL, Sokoll MD, Gergis SD, et al: Relative effects of streptomycin on motor nerve terminal and end-plate. Eur J Pharmacol 22:10–16, 1973
47. Van Nyhuis LS, Miller RD, Fogdall RP: The interaction between *d*-tubocurarine, pancuronium, polymyxin B, and neostigmine on neuromuscular function. Anesth Analg 56 (March), 1976
48. Fogdall RP, Miller RD: Prolongation of a pancuronium-induced neuromuscular blockade by polymyxin B. ANESTHESIOLOGY 40: 84–87, 1974
49. Fogdall RP, Miller RD: Prolongation of a pancuronium-induced neuromuscular blockade clindamycin. ANESTHESIOLOGY 41:407–408, 1974
50. Telivuo L, Katz RL: The effects of modern local analgetics on respiration during partial neuromuscular block in man. Anaesthesia 25:30–35, 1970
51. Usubiaga JE, Wikinski JA, Morales RL, et al: Interaction of intravenously administered procaine, lidocaine and succinylcholine in anesthetized subjects. Anesth Analg (Cleve) 46:39–45, 1967
52. Miller RD: Factors affecting the action of muscle relaxants, Muscle Relaxants. Edited by RL Katz. Amsterdam, Excerpta Medica, 1975, pp 163–191
53. Harrah MD, Way WL, Katzung BG: The interaction of *d*-tubocurarine with antiarrhythmic drugs. ANESTHESIOLOGY 33:406–410, 1970
54. Miller RD, Way WL, Katzung BG: The neuromuscular effects of quinidine. Proc Soc Exp Biol Med 129:215–218, 1968
55. Johnston RR, Miller RD, Way WL: The interaction of ketamine with neuromuscular blocking drugs. Anesth Analg (Cleve) 53:496–501, 1974
56. Cronnolly R: Interaction of ketamine HCl with neuromuscular agents (abstr). Fed Proc 31: 535, 1972
57. Dretchen K, Ghoneim MM, Long JP: The interaction of diazepam with myoneural blocking agents. ANESTHESIOLOGY 34:463–468, 1971 468, 1971
58. Gissen AJ, Katz RL, Karis JH, et al: Neuromuscular block in man during prolonged arterial infusion with succinylcholine. ANESTHESIOLOGY 27:242–249, 1966
59. Katz RL, Ryan JF: The neuromuscular effects of suxamethonium in man. Br J Anaesth 41: 381–390, 1969
60. Galindo A: Depolarizing neuromuscular block. J Pharmacol Exp Ther 178:339–349, 1971
61. Miller RD, Stevens WC: Antagonism of succinylcholine paralysis in a patient with atypical pseudocholinesterase. ANESTHESIOLOGY 36:511–513, 1972