ANESTHESIA IN THE PATIENT WITH MYASTHENIA GRAVIS

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CLINICAL FEATURES OF MYASTHENIA GRAVIS

MYASTHENIA gravis is a chronic disease of uncertain etiology, characterized by its tendency to spontaneous remission and exacerbation. Though frequently stated to be most common in white females in the third decade of life, its occurrence in the aged and children is not uncommon. Cranial nerve involvement is almost always present, especially as manifested by ocular ptosis, dysphagia, and ready fatigue of the masseters. Physical examination reveals little evidence of atrophy or reflex change. A return of normal muscle strength following rest, with the onset of muscular weakness on exercise, is the most reliable feature of the clinical history. In the more serious cases, muscle groups most seriously involved may not regain strength, even after prolonged rest.

CHEMICAL DIAGNOSIS OF MYASTHENIA GRAVIS

Diagnosis of myasthenia gravis in the patient who presents classical symptoms is not difficult. It is in the borderline case which, if unrecognized, can give rise to grave anesthetic complications that we must rely most heavily on chemical tests. Shortly after Walker described the effects of neostigmine in the myasthenic, Viets and Schwab (1) utilized it as a confirmatory diagnostic test. Muscle strength improves within five minutes after injecting 1.5 mg. of neostigmine and 0.4 to 0.6 mg. of atropine, intramuscularly.

A number of drugs which will aggravate the conduction defect have also been used; namely, quinine (2), d-tubocurarine (3), and gallamine (4). Recently Osserman and Kaplan (5, 6) have studied the use of edrophonium (Tensilon®) chloride with encouraging results; especially desirable is the lack of side effects. Two milligrams are given intravenously, and if improvement in muscle strength without fasciculation is not noted within one minute, a second dose of 8 mg. is given. False positives have not been reported.

THE PATHOPHYSIOLOGY OF THE NEUROMUSCULAR JUNCTION IN MYASTHENIA GRAVIS

The end-plate region has been morphologically explored by Couteaux (7), utilizing supravital staining with Janus green. Structures

have been noted separate from the terminal arborization of the nerve, which are rod-like masses arranged in palisades perpendicular to the nerve terminals. The enzyme, acetylcholinesterase, has been histologically localized at the rods (8, 9). Separating these from the nerve terminals is the teloglial sheath.

In order to appreciate the abnormality of neuromuscular transmission in myasthenia gravis, one can accept the following as the normal mode of transmission. Acetylcholine is generally agreed to be the all-important link in the transmission of the nerve impulse across the myoneural junction (10). Upon the arrival of a motor nerve impulse at the end-plate, acetylcholine is liberated from an inactive bound precursor (11). Apparently the attachment of acetylcholine molecules to the motor end-plate alters permeability so that ions previously lined up in the polarized state can cross the membrane, thus depolarizing
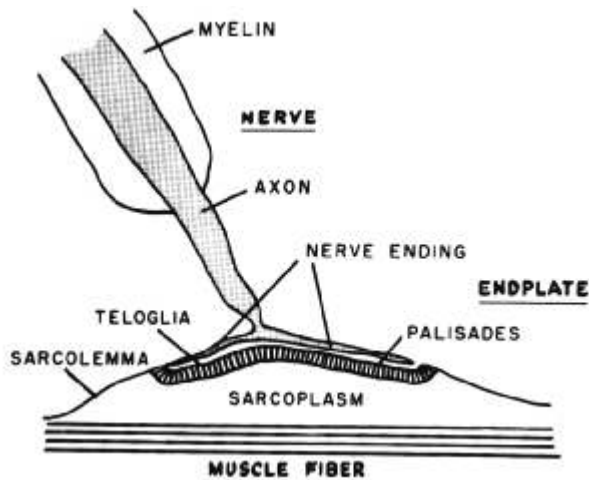

FIG. 1.   The myoneural junction.

the end-plate (12). This end-plate potential can be recorded as distinct and preceding muscle depolarization (13). End-plate potential must reach a critical level before it is propagated to muscle, though this is only 30 per cent of normal end-plate potential (13). Muscle depolarization is followed by muscle contraction. At the end-plate, the acetylcholine has been rapidly hydrolyzed into choline and acetic acid, and resting potential across the membrane has been restored. Another enzyme, cholineacetylase, brings about resynthesis of acetylcholine in the bound form (9). This can be summarized as shown in figure 2.

Impairment of the neuromuscular junction can theoretically be brought about in a number of ways, and each of the following has been suggested at one time as the basic defect in myasthenia gravis: (1) decreased release of acetylcholine, (2) competition with acetylcholine by a "curariform" substance for end-plate receptors, (3) hyperactivity

of cholinesterase, (4) excess of acetylcholine, and (5) aberrant response or condition of muscle end-plate.

In favor of a decreased quantitative production of acetylcholine is the work of Harvey (14) in which acetylcholine injected intra-arterially transiently depresses muscle action potentials induced by nerve stimulation. This is followed by a temporary correction of the myasthenic deficit, lasting one to two minutes. This would suggest that myasthenia is due either to a decreased release of transmitter substance (acetylcholine) or to block of the normal transmitter effect at the end-plate. Inasmuch as the blockade of curare is not so readily offset by intra-arterial acetylcholine, it was reasoned that if the defect in myasthenia were due to a blockade similar to that of curare, it would not have been so readily reversed by acetylcholine. This does not necessarily follow because the response to anti-cholinesterase drugs or acetylcholine varies with the degree of curarization and time.

**NORMAL PATHWAY
TO MUSCULAR CONTRACTION**

NERVE IMPULSE

ACETYLCHOLINE
from precursor

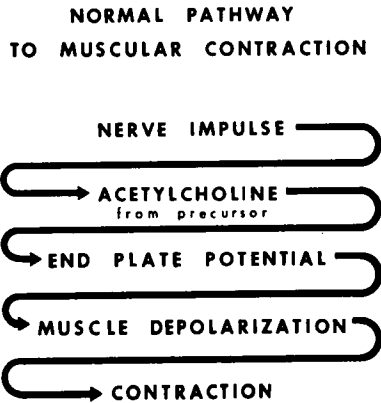END PLATE POTENTIAL

MUSCLE DEPOLARIZATION

CONTRACTION

FIG. 2. Normal pathway to muscular contraction.

The evidence in favor of a curare-like mechanism is confusing. Torda and Wolff (15) claim that ether extract of the thymus and pancreas of the cat decreases acetylcholine synthesis *in vitro* and that other organ extracts have no demonstrable effect. Trethewie and Wright (16), utilizing Torda and Wolff's technique, found that extract of the thymus of a myasthenic decreased acetylcholine synthesis, while extract from two nonmyasthenic newborns increased it. The occurrence of transitory myasthenia of the newborn is used as an argument in favor of a circulating curare-like substance. Schwarz (17) has transfused up to 1,500 cubic centimeters of blood from severe myasthenics into normals with no evidence of weakness. There is little evidence to support hyperactivity of cholinesterase or excess acetylcholine production.

The general line of thought at the present time appears to be swinging toward aberrant response or an end-plate abnormality. Zaimis (18) noted that decamethonium produced a depolarization block in the

cat and man; but that in the monkey, dog, and hare the block differed in
many ways from one of pure depolarization in that tetanus was poorly
sustained and anticholinesterases opposed the block. She has sug-
gested that decamethonium and succinylcholine have a dual mode of
action, in that the molecule first adheres in such a way to produce
depolarization, and then the stearic relation changes to one that pro-
duces nondepolarization block. The idea is strengthened by the obser-
vation that tridecamethonium produces a nondepolarization type block
in the cat, while decamethonium produces a depolarization block. This
shows that stearic relations can play a role in end-plate response to a
drug. The concept of a dual mode of action of blocking agents is ex-
tended to the myasthenic end-plate by observations on the effect of de-
camethonium in myasthenics and normals. Churchill-Davidson and
Richardson (19), in their study, showed widespread paralysis in six
normals following the injection of 2.5 mg. of decamethonium iodide and
a marked fall in action potentials of the hypothenar eminences; while
12 myasthenics showed only slight degrees of paralysis, and the hypoth-
enar action potentials were sustained. The characteristics of nonde-
polarization block are rapid failure of tetanic stimulation, unaffected
response to twitch until marked paralysis supervenes, and reversibility
by neostigmine and edrophonium. In the normal subject given deca-
methonium, neostigmine aggravates the block; and twitch and tetanus
are equally affected, thus demonstrating a depolarization block. In the
myasthenic who is relatively refractory to decamethonium, increasing
doses will first affect the muscles showing most clinical evidence of in-
volvement; and the paralysis will be much longer than normal, however,
it is dramatically reversed by anticholinesterases, and is greater for
tetanus than twitch. This dual mode of action could be due to changes
in the drug itself or an altered mode of end-plate response. Zaimis
has shown that decamethonium is excreted in urine unchanged by
myasthenics so that we are left with the hypothesis of altered end-plate
response. With these facts in mind, it has been postulated that myas-
thenia gravis which has all the characteristics of a nondepolarization
block may be due to an abnormal response of the end-plate to acetyl-
choline or its metabolites, producing a combination with receptor pro-
tein that raises the excitation threshold and produces a nondepolariza-
tion block (18–21). Grob, Johns, and Harvey (22) feel that there is an
abnormal response to the choline liberated as a result of acetylcholine
hydrolysis. They present evidence that choline administered intra-
arterially can produce conduction abnormality in a myasthenic, but not
in a normal.

EFFECTS OF RELAXING AGENTS AND ANESTHETICS ON THE NEUROMUSCULAR JUNCTION OF MYASTHENICS

At present the agents producing neuromuscular blockade are best
classified as shown in table 1. This classification is adequate for clini-

cal use at present and will likely remain so until Thesleff's (23) work has been extended and confirmed. There are no relaxants in present clinical use producing deficiency block.

Inasmuch as myasthenia gravis shows many of the characteristics of a nondepolarizing block, one would expect a hypersensitivity to drugs of this group, and such is the case. Bennett and Cash (24) utilized the hypersensitivity of myasthenics to curare as a diagnostic test. Pelikan, Tether, and Unna (25), have shown a sensitivity to curare up to twenty times that of normals. Dundee (26) has demonstrated hypersensitivity to gallamine. Bergh (27) has corroborated both studies. In the depolarizing group, decamethonium is, of course, well known for its dual mode of action on the myasthenic end-plate (18–21). It produces a paralysis which is prolonged and reversed by anticholinergics once the initial tolerance to the drug is overcome.

Succinylcholine has not as yet been demonstrated to act any differently on the myasthenic end-plate than normals (27). For some time,

TABLE 1

TYPES OF NEUROMUSCULAR BLOCKADE

Deficiency Block	Nondepolarization Block
Calcium deficiency	D-tubocurarine
Botulinus toxin	Laudolissin
Procaine	Mytolon
	Gallamine
Depolarization Block	
Decamethonium	Dual Block
Succinylcholine	In myasthenics and
	occasionally in normals

anesthesiologists have made the statement that "ether has a curare-like action," yet there has been no proof. The detailed studies of Secher (28, 29) should leave no doubt that ether has a peripheral action. In addition to re-eliciting contractions of the ether paralyzed phrenic-diaphragm preparation by adding neostigmine to the bath, he has also lead normal action potentials from the nerves at a time when indirectly stimulated contractions have been blocked by ether. The other anesthetic agents, with the exception of chloroform, have little blocking activity in clinical concentrations (30). The adjunctive drug, quinidine, does depress muscular contraction.

While Harvey (31) has shown a peripheral action of procaine, no untoward results have been reported when local anesthetics were used in moderation. Laboratory studies have also shown normal esterase levels in myasthenics, therefore, local anesthetic agents should be hydrolyzed at normal rates.

PREOPERATIVE PREPARATION

In addition to the routine history, physical and complete blood count, there are certain ancillary investigations which may decrease

the risk for the patient. Serum potassium determination should be done in all cases of questionable electrolyte balance since hypokalemia aggravates myasthenia. A chest roentgenogram will demonstrate any abnormal preoperative pulmonary pathology and also may be used for comparison with postoperative films.

In view of recent pathological studies by Mendelow and Genkins (32) demonstrating cardiac lesions in twelve autopsy cases, it would be well to have a preoperative electrocardiogram and cardiac evaluation. These workers have demonstrated areas of myocardial necrosis with secondary inflammatory reaction, being most marked in the cases associated with thymoma.

Our group in the past has felt strongly about preoperative vital capacity determinations to serve as a reference standard, though the quadrant plot of 0.5 second expiratory capacity/total vital capacity against per cent predicted total vital capacity as recently advocated by Miller, Wu, and Johnson (33) is probably more accurate. Just as one can demonstrate decreasing tidal volumes in the polio patient approaching respiratory crisis, one can predict and prevent difficulties in the myasthenic. It is of interest that in Bergh's (34) series all the patients who died had vital capacities of less than 1,000 cubic centimeters when not receiving specific therapy. If the situation is one not requiring immediate intervention, it is well to correct protein and vitamin deficiencies.

The presence of respiratory infection of even minor degree contraindicates all but the most urgent surgery. Should intervention have to be performed in the face of respiratory infection, the use of broad spectrum antibiotics is advised.

There is a striking similarity between diabetes mellitus and myasthenia in that both are controlled by accurately adjusting the dosage of a drug and both are aggravated by fatigue and intercurrent infection. The myasthenic coming to elective surgery should be carefully regulated on oral neostigmine for ten days or two weeks, until the optimum dosage is reached. Fortunately the advent of the edrophonium (Tensilon) test has simplified regulation. Osserman (35) has classified the types of response to the intravenous injection of edrophonium as adequate, myasthenic, and cholinergic. In the myasthenic reaction, there is evidence of increased muscle strength without fasciculations or side reactions. A cholinergic response is characterized by decrease of strength, as noted by examiner and patient; side reactions in the form of lacrimation, diaphoresis, salivation, abdominal cramps, nausea, vomiting, and diarrhea, which may vary from mild to severe; and fasciculations which are usually, but not always, present. The adequate response is the same as seen when edrophonium is given to a normal; there are fasciculations, mild side reactions, and no change in muscle strength.

The test can be done serially at hourly intervals in the severe or

brittle myasthenic; however, in the average case, a single test two hours after the previous dose of neostigmine is adequate. This test is certainly of great value in the management of respiratory crisis in which it is possible to rapidly determine whether the respiratory insufficiency is due to myasthenia or a cholinergic crisis.

Premedication should be kept at a minimum, avoiding morphine and barbiturates because of an apparently lowered tolerance (34). Demerol in half the usual dose should be adequate. Females are best operated on postmenstrually, as their myasthenia shows cyclic variation (34).

OPERATIVE MANAGEMENT

The selection of anesthetic agents and techniques for the myasthenic revolves around the prevention of prolonged respiratory depression and the maintenance of adequate alveolar ventilation throughout the procedure.

Procedures below the umbilicus can readily be carried out under spinal analgesia with little danger to the patient, however, spinal analgesia should not be be given to levels which might prevent adequate pulmonary ventilation. Though Harvey (31) has demonstrated the neuromuscular blocking properties of procaine, we have had no untoward effects when used in moderate doses for regional block; and Bergh (34) has used it uneventfully.

The choice of agents for general anesthesia is unsettled; however, it would seem advisable in light of Secher's (28, 29, 30) work demonstrating neuromuscular blockade with ether to avoid this agent entirely or use it sparingly. While there are cases that have been managed with thiobarbiturates, the number of case reports of prolonged apnea or respiratory depression following their administration to the myasthenic speaks against their use, as does their slow rate of dissipation from the body. Of the inhalation agents, cyclopropane stands as the agent of choice in that it is rapidly eliminated and also capable of producing all levels of anesthesia without supplementation. Almost any procedure can be satisfactorily carried out with endotracheal cyclopropane and oxygen in the absence of relaxants. Should relaxants become necessary, all the nondepolarizing group are contraindicated; and succinylcholine is the drug of choice. When administering succinylcholine to the myasthenic, it is well to bear in mind the possibility of two-stage hydrolysis and the possible accumulation of succinylmonocholine, which is slowly dissipated and has weak ability to produce neuromuscular blockade. The previous, plus the findings of Grob (22) that choline can aggravate myasthenia when given intra-arterially, should prompt one to use as little succinylcholine as possible, though it is most likely that concentrations of choline approaching that of direct intra-arterial injection never occur clinically.

Few authors would attempt to carry out a general anesthetic pro-

cedure in the presence of myasthenia gravis without endotracheal in-
tubation, unless the procedure were going to be extremely short. In-
asmuch as the maintenance of a clear and unobstructed airway and the
ability to adequately eliminate secretions are necessary to the anes-
thetic management of these cases, we feel that provision of a direct
route to the tracheo-bronchial tree for gas exchange and suction more
than outweighs any disadvantages. If the airway is maintained, and
ventilation is adequate, the accumulation of carbon dioxide will not
occur, thus eliminating its additive depressant effects and tendency to
produce bronchiolar constriction.

There are differences of opinion as to whether specific therapy
should be given during or immediately before the operative procedure.
Some maintain that with endotracheal intubation and the facilities for
positive pressure respiration, one need not fear inadequacy of the re-
spiratory muscles and that bronchorrhea, due to the neostigmine will
merely add to postoperative difficulties. We take the opposite stand
and feel that these people should be maintained as near physiologic as
normal. For this reason, assisted rather than controlled respiration
is our aim. It is a simple matter to utilize the technique of Viets (36)
for converting oral neostigmine dosage to intravenous. The twenty-
four hour oral requirement is divided by three, then for each 15 mg. of
oral neostigmine used in eight hours, 0.5 mg. of Parenteral is added to
1,500 cc. of 5 per cent glucose which is so regulated as to drip evenly
over an eight-hour period. While any one institution or group's ex-
perience with myasthenia is small, we have used neostigmine to slow
the pulse in many patients for mitral commissurotomy and have had no
excessive bronchial secretions. Should excessive secretions occur, they
should be promptly aspirated. The possibility of the use of an edro-
phonium drip in place of neostigmine has to our knowledge not been
explored, but its rapid elimination and relatively low toxicity suggests
further study along these lines.

POSTOPERATIVE CARE

If one reviews the slightly over three hundred well-reported cases
of thymectomy in the myasthenic, it becomes readily apparent that al-
most every death was due to a postoperative pulmonary complication
(34, 37, 38, 39). The meticulous utilization of minimal amounts of an-
esthetic agents and adequate tracheal toilet throughout the procedure
is the first step in lessening complications. The patient who has his
cough reflex and is awake at the end of the procedure is a goal to be
aimed for.

The patient is transferred to a room with facilities for adequate
suction and a means of giving oxygen under pressure. A mechanical
tank respirator or pulmonary ventilator and a tracheotomy set are
ready for instant use. Special nurses are present around the clock to
aspirate secretions and follow vital signs. If pharyngeal suction is

not adequate, aspiration bronchoscopy is performed without hesitation. Should it become apparent that repeated bronchoscopies will be necessary or there is difficulty in suctioning secretions, a tracheotomy is done. Those who have handled cases following head and neck surgery will appreciate the advantages in terms of reduction of anatomical dead space and ease of elimination of secretions afforded by tracheotomy. Serial vital capacity determinations are done; and in the presence of a falling vital capacity, tracheotomy is done and the patient placed in a tank respirator or connected to a mechanical ventilator. Adequacy of ventilation is measured by determination of pCO_2.

Most myasthenics will show increased neostigmine requirements postoperatively. When there is muscular weakness or evidence of inadequate ventilation, the edrophonium (Tensilon) test is used serially to insure optimum adjustment of neostigmine dosage. Antibiotics are given prophylactically and frequent movement and deep breathing are encouraged.

Patients who by virtue of their surgical procedure or postoperative gastric suction might develop electrolyte imbalance are carefully followed with special emphasis on serum potassium levels.

SUMMARY

The salient clinical features and the chemical diagnosis of myasthenia gravis have been discussed. The basic physiology of the neuromuscular junction is described, and the effects of ether, d-tubocurarine, and the depolarizing relaxants are noted. Ether and chloroform have neuromuscular blocking properties similar to curare. In the myasthenic and possibly at times in the normal, decamethonium can exert a dual action and function as a nondepolarizing relaxant. Myasthenics tend to be extremely sensitive to nondepolarizing relaxants. They should be carefully regulated on oral neostigmine before coming to surgery. During surgery the oral dose can be converted to a parenteral one. The avoidance of muscle relaxants, unless absolutely necessary, is imperative. Should they be necessary, succinylcholine is the drug of choice.

Throughout the operative procedure and postoperative period, rigid attention to ventilation, the maintenance of a patent airway, and the removal of secretions are paramount to patient safety. Aspiration bronchoscopy or tracheostomy and the use of mechanical ventilating devices should be employed without hesitation if there is difficulty in removing secretions or ventilation is inadequate. Serial determinations of pulmonary function and the use of the edrophonium test in regulating neostigmine dosage are advocated.

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