

2005 CE Series - Lesson Ten

Myasthenia Gravis & Its Treatment

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Goals and Objectives

Goals: To provide the pharmacist with information regarding myasthenia gravis and its treatment.

Objectives: After completing this article, the pharmacist should be able to:

1. Describe the normal physiology regarding the neuromuscular junction.
2. Review the theories associated with the etiology of myasthenia gravis.
3. Discuss the treatment regimens and rationale for their use in myasthenia gravis.
4. Discuss the drugs used in myasthenia gravis.
5. Counsel patients with regard to their treatment program for myasthenia gravis.

Myasthenia gravis is a chronic autoimmune disease that derives its name from Latin and Greek words meaning “grave muscle weakness”. Myasthenia gravis is associated with neuromuscular dysfunction and characterized by weakness and fatigue of the voluntary skeletal muscles. It may affect any muscle, but those of the face and throat are more commonly involved. The muscle weakness often oscillates over periods of days or weeks and remissions and relapses may occur over longer periods of time.

EPIDEMIOLOGY

Myasthenia gravis is not a common disease. Its incidence among the general population is approximately 2 per 10,000 in the United States. However, it is possible that many cases are undiagnosed. Therefore, it is difficult to ascertain whether these statistics are correct.

The onset of symptoms occurs most frequently between the ages of 20 and 35 years. Females within this age group are more commonly affected. However, in individuals over 50 years of age and in children, both sexes are equally affected.

Although myasthenia gravis does not appear to be hereditary, between 10% and 15% of the children born to myasthenia gravis mothers suffer from neonatal myasthenia gravis. Fortunately, this condition lasts only for a few weeks.

Several diseases are associated with myasthenia gravis. These include rheumatoid arthritis, thyroiditis, and systemic lupus erythematosus. This association has resulted in additional evidence for an autoimmune etiology for myasthenia gravis which is the accepted theory.

NORMAL NEUROMUSCULAR JUNCTION ACTIVITY

Since the major pathology of myasthenia gravis involves abnormal activity at the neuromuscular junction, it is important to review the normal physiology of this area.

The physiological transmitter is acetylcholine which is released in packets in response to the nerve action potential. Transmission of action potentials on motor nerve impulses to striated muscle occurs at the neuromuscular junction. At this point, the nerve fiber expands and fits into the motor end plate on the muscle cell membrane. A narrow synaptic space separates the muscle and nerve.

Resting muscle cells are electrically polarized such that the exterior is positively charged with respect to the interior because of higher extracellular concentrations of potassium ions. When a nerve action potential reaches the junction of the motor end nerve fiber, packets of acetylcholine are released. This release depends in part on adequate calcium ion concentration. If a sufficient amount of acetylcholine is released and reaches the receptors on the motor end place, a rapid shift of potassium and sodium ions across the muscle cell membrane occurs because of increased permeability. This causes depolarization of cells which spreads throughout the muscle and results in contraction.

Acetylcholinesterase rapidly inactivates acetylcholine and initial ionic gradients recur which results in muscle repolarization.

The actions of acetylcholine on skeletal muscle differ from those on smooth muscle (i.e., increased salivation and GI motility). Anticholinergic drugs (atropine) block the smooth muscle effects, but have minimal or no effects on the skeletal muscle activity of acetylcholine.

ETIOLOGY OF MYASTHENIA GRAVIS

Myasthenia gravis was initially described by Thomas Willis in 1672. However, no effective treatment was known until approximately sixty years ago. In 1934, Mary Walker administered physostigmine to a patient and a dramatic improvement occurred. This was a milestone in uncovering the riddles associated with myasthenia gravis.

For many years the etiology of myasthenia gravis was attributed to impaired synthesis and/or storage of acetylcholine. This would, in effect, reduce the amount of acetylcholine in each packet. Modern technology has revealed additional information which indicates that myasthenia gravis results from damage to the motor end plate membrane and its acetylcholine receptors by autoimmune mechanisms. Electron microscopy has demonstrated that the acetylcholine-containing vesicles at the end of the neuron are at normal size, but the motor end place is abnormal and the number of acetylcholine receptors is decreased in the patient with myasthenia gravis.

The abnormalities at the motor end plate are probably the result of autoimmune processes. It has been demonstrated that many individuals with myasthenia gravis have measurable amounts of circulating polyclonal AchR-binding autoantibodies. These antibodies appear to be specific to patients with myasthenia gravis, but do not have good correlations with severity of the disease. The exact mechanism of autoimmune activity is unclear, but several processes may be involved which may also relate to the fluctuating clinical course of the disease in different patients.

DRUG INDUCED NEUROMUSCULAR BLOCKADE

A variety of drugs have been implicated in causing an aggravation of muscular weakness and/or a syndrome similar to myasthenia gravis. Aminoglycoside antibiotics (i.e., gentamicin, tobramycin)

cause a pharmacologic neuromuscular blockage by interfering with acetylcholine release. Quinine, quinidine, and procainamide also have a similar effect with regard to acetylcholine.

Although they do not appear to act at the neuromuscular junction, penicillamine, busulfan, and trimethadone have been associated with symptoms resembling myasthenia gravis. However, when the drugs are discontinued, the symptoms usually disappear.

Numerous other drugs should be administered with caution to patients with myasthenia gravis. Central nervous system depressants, particularly narcotic analgesics and barbiturates, may impair neuromuscular activity. Diuretics, such as furosemide or the thiazides, may cause hypokalemia and resulting muscle weakness. In general, any drugs or ions (i.e., magnesium, which may be a component of antacids) which affect neuromuscular transmission and/or muscle function should be administered with caution to patients with myasthenia gravis.

CLINICAL FEATURES

The most common symptom is muscle weakness without pain or atrophy. However, the patient may complain of muscle ache which is common in any fatigued muscle. The ocular muscles are mostly commonly affected. Double vision (diplopia) and drooping of the eyelids (ptosis) are typical symptoms. In approximately 30% of the patients, weakness is limited to this area.

Facial and oropharyngeal muscles are frequently involved in the early phases of the disease. In some cases, it is difficult to chew, speak, and/or swallow. The patient's voice may become a whisper as speech continues and the smile may fade into the exact opposite expression because of lack of facial muscle strength and control.

Peripheral muscle weakness is not as common and occurs primarily in the advanced disease. If this occurs, the patient will develop gait disturbances and have difficulty with typical daily tasks (i.e., hair combing, teeth brushing).

The specific symptoms are somewhat variable because the course of the disease varies. In most instances, the onset may be gradual with symptoms progressing to a certain point where they remain for several years. At this point, there may be exacerbations and remissions, or there may be a long term remission. In other cases, the disease may progress very rapidly during a six-month period from weakness in ocular or facial muscles to proximal limb muscles to distal limb muscles and, finally to respiratory muscles, which results in death.

DIAGNOSIS

If a diagnosis of myasthenia gravis is suspected, then specific tests for confirmation can be utilized. The patient can be instructed to count aloud as far as possible after taking one large breath. Normal adults will count to approximately 50, while the patient with myasthenia gravis may need to take a breath by 15. The patient may also develop a nasal quality in the voice during the procedure. Other tests of muscle fatigue, such as lifting the head off the pillow repeatedly, looking upward without blinking, hand gripping and leg raising, will also demonstrate muscle weakness.

Two significant diagnostic procedures can be used. An electromyogram, a test which records the responses of muscles to electrical stimulation of a motor neuron, can be used to evaluate muscle weakness. In normal individuals, the muscle responds similarly with each stimulation, while the individual with myasthenia gravis will experience a decrease in muscle response.

The “Tensilon test” can also be used. In this case edrophonium chloride, an injectable acetylcholinesterase inhibitor with a rapid onset and brief duration of action, is used to evaluate cranial and ocular muscle weakness. Before the drug is administered, muscle strength is evaluated (i.e., ptosis, voice, etc.). Then, muscle strength evaluation is made within one minute after intravenous doses of two and eight milligrams of edrophonium. The myasthenia gravis patient appears to have normal muscle strength for a brief period, then the drug effects disappear. This procedure must be carefully supervised because too rapid administration of the drug can cause severe adverse effects, even cardiovascular collapse. A similar procedure can be used by administering 1.5 milligrams of neostigmine intramuscularly. This response will last for about two hours. Atropine should be available to reverse the muscarinic side effects.

Single Fiber EMG is the most sensitive clinical test of neuromuscular transmission and shows increased jitter in some muscles in almost all patients with myasthenia gravis. Jitter is greatest in weak muscles but may be abnormal even in muscles with normal strength. Patients with mild or purely ocular muscle weakness may have increased jitter only in facial muscles. Increased jitter is a nonspecific sign of abnormal neuromuscular transmission and can be seen in other motor unit diseases. Normal jitter in a weak muscle excludes abnormal neuromuscular transmission as the cause of weakness.

Identification of measurable titers of anti-AchR is increasingly used as a diagnostic tool for myasthenia gravis. The assay process and results have become more reliable. Once the diagnosis is established, the severity of myasthenia gravis can be staged using the Osserman classification system. This staging process uses various symptoms and severity of symptoms to establish a general prognosis for the patient. (Table 1)

DRUG THERAPY

Although there have been advances in the treatment of myasthenia gravis, anticholinesterase drugs are still the initial treatment most commonly employed. These drugs make more acetylcholinesterase available to receptors at the neuromuscular junction by inhibiting acetylcholinesterase. Therefore, there is increased neuromuscular transmission regardless of the etiology of the disease. The drugs most frequently used are pyridostigmine and neostigmine. A third drug, ambenonium, is occasionally used.

Pyridostigmine is most frequently used for maintenance treatment of myasthenia gravis. It is well tolerated and usually produces few undesired adverse effects. The usual oral dose is 60 milligrams in tablet or syrup form. The syrup is beneficial for many myasthenia gravis patients who have difficulty swallowing. A long-acting dosage form is also available, but is often more variable in effect. Pyridostigmine has very low oral bioavailability (8%) and a half-life of about 1.5 hours.

Neostigmine is shorter-acting (two to three hours) than pyridostigmine (four to six hours). It is administered in an oral dose of 15 milligrams every three to five hours. Frequently, dosing intervals must be increased which can result in poor compliance. Neostigmine is also available in a parenteral dosage form, but this is used primarily for diagnosis and very severe cases. Neostigmine has very low oral bioavailability (2%) and a half-life of about an hour. Like pyridostigmine, the peak plasma concentration following a fasting oral dose is approximately 1.5 hours.

There are a variety of problems associated with the use of cholinesterase inhibitors. Typical cholinergic effects, such as diarrhea, bradycardia, and miosis, occur in many patients. Neostigmine appears to cause these most often. In some instances, these effects can be controlled with atropine (0.4 - 0.6 milligrams two to four times a day). Response to these drugs is variable among, and even within patients. Different muscle groups within a patient may react differently to the drug. For example, some degree of ocular weakness may be present in order to avoid cholinergic paralysis of respiratory muscles. Ocular symptoms, particularly diplopia which requires specific coordinated muscle control, are difficult to control.

Another important feature is adequate dosage regulation. Dosage adjustments must be evaluated frequently and made carefully. It is essential that adequate treatment be administered, but overdose can result in cholinergic crisis manifested as increased weakness which may mimic myasthenia gravis. If this is suspected, then small doses (i.e., two milligrams) of edrophonium can be administered just prior to the next scheduled dose. If a dramatic increase in strength is demonstrated, it is an indication that more frequent and larger doses are required, while a decrease or no change in muscle strength and occasional cholinergic side effects are encountered as indications of possible overdose.

The anticholinesterase drugs are not curative and do not alter the pathologic progression of the immune process of the motor end plate. These drugs are most beneficial in mild generalized disease where the rapid onset of effects is valuable.

Several drugs increase the force of responses within single muscle fibers. In those fibers that can respond, the muscle action potential is prolonged. Caffeine and ephedrine exhibit this activity. Unfortunately, the response of the muscle requires a contraction rather than a twitch effect. Therefore, these drugs are not very beneficial.

Potassium supplements and calcium salts are also used because of their respective effects on electrical activity at nerve and muscle tissue, causing appropriate release of acetylcholine. However, their effects are minimal. Potassium sparing diuretics (i.e., spironolactone) have also been used, but they are expensive and their effectiveness is unimpressive.

Corticosteroids have been used to treat myasthenia gravis for approximately sixty years. Their specific mechanism of action is not clearly understood. These drugs appear to protect the AchR from the effects of autoantibodies as well as provide antiinflammatory effects. Corticosteroids are effective at any stage of myasthenia gravis, but are usually used in patients with severe symptoms who have not responded well to large doses of anticholinesterase drugs. A variety of therapeutic regimens have been used. These include a high dose regimen (e.g., prednisone in a 60 mg to 80 mg daily dose until a response is seen, then dose on alternate days) and a low dose regimen (e.g., prednisone in low daily doses). The benefits are usually not seen for approximately one month. There are numerous adverse effects associated with corticosteroid therapy, including peptic ulcer disease, diabetes mellitus, cataracts and hypertension. Parenteral corticosteroids (e.g., methylprednisolone in intravenous pulse doses of 2 grams at five day intervals) have been beneficial in some patients, particularly those with disease exacerbation.

A variety of immunosuppressive agents have been employed in the management of myasthenia gravis. Azathioprine is the most frequently used drug, but cyclophosphamide, mercaptopurine, and methotrexate have also been useful in some patients. The specific mechanism of action of these drugs is not clear, but they appear to decrease the number of circulating antibodies directed

toward AchR. Immunosuppressives are used primarily in patients who have not been adequately controlled with anticholinesterase drugs. In some instances, immunosuppressives have been used in combination with corticosteroid drugs which allows for a reduction in corticosteroid dosage. A variety of adverse effects occur with immunosuppressives, including bone marrow suppression, hepatic dysfunction, gastrointestinal intolerance, and rash.

Cyclosporine and intravenous immunoglobulin have been used to treat myasthenia gravis in patients who do not respond to other forms of therapy. Cyclosporine exerts its effects within a month, but does have nephrotoxic activity which must be monitored. Cyclosporine acts by inhibiting the synthesis and release of lymphokines which have an influence on clonal expansion and T-helper cells. Therefore, cyclosporine affects cellular immunity which may have a role in the pathogenesis of myasthenia gravis.

Intravenous immunoglobulin has been used in high doses for short periods which has resulted in moderate success of improving muscle strength. The exact mechanism of action of intravenous immunoglobulin is unknown.

In all situations, the patient must be carefully monitored with regard to the benefits and risks associated with the specific therapeutic program.

THYMECTOMY

Thymectomy or surgical removal of the thymus usually provides symptomatic benefit or remission and should be undertaken in patients younger than age 60, unless weakness is restricted to the extraocular muscles. If the disease is of recent onset and only slowly progressive, then thymectomy may be delayed.

The thymus plays a role in immunological processes. Thymomas appear to be more common in patients with myasthenia gravis. These factors provide further support for thymectomy in patients with myasthenia gravis.

Although the technique is greatly improved, thymectomy requires a specialized treatment team and a long and complex postsurgical management, particularly in this type of patient who may have respiratory problems. Thymectomy should not be performed on the very old or young or in those patients that are only afflicted with the ocular form of myasthenia gravis.

PLASMA EXCHANGE

Plasma exchange has provided improvement in many patients with myasthenia gravis. There is usually marked improvement in half the patients between the first and fourth exchange and almost all patients receive some benefit by the fifteenth exchange. Unfortunately, the improvement usually lasts from one to twelve weeks and the procedure is complex. Plasma exchange is also valuable when patients have respiratory distress problems related to myasthenia gravis.

COMPLICATIONS OF MYASTHENIA GRAVIS

The major complications of myasthenia gravis are cholinergic and myasthenic crises. Respiratory paralysis associated with muscle weakness is the major concern in each case.

Myasthenia crisis results from an acute exacerbation of the disease which can occur because of decreased response to therapy, respiratory infections, and/or poor compliance with treatment programs. Cholinergic crisis results from an overdose of anticholinesterase drugs.

These patients require immediate treatment (particularly for any respiratory involvement) and are usually placed in an intensive care unit. The patient should be stabilized and then the exact source of the crisis can be evaluated.

SUMMARY AND CONCLUSIONS

Myasthenia gravis is an uncommon disease. Although there is no cure, most patients improve significantly with treatment. The newer immunological approaches to therapy in association with proper management and supportive care can frequently provide a reasonably complete and normal existence for many individuals with myasthenia gravis.

Since myasthenia gravis requires maintenance drug therapy, the pharmacist may frequently be of assistance regarding counseling these patients to properly use their drugs and evaluating potential adverse effects.

Bibliography

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Table 1.

Osserman's Classification of Adult Myasthenia Gravis *

- I. Ocular myasthenia**
- II. Generalized myasthenia**
 - A. Mild, generalized myasthenia with slow progression; no crises; drug-responsive**
 - B. Moderate, generalized myasthenia; severe skeletal and bulbar involvement, but no crises; drug response less than satisfactory**
- III. Acute fulminating myasthenia; rapid progression of severe symptoms with respiratory crises and poor drug response; high incidence of thymoma; high mortality**
- IV. Late severe myasthenia, same as class III but with progression over two years from class I to II**

** Adapted from Osserman KE: Myasthenia Gravis, Grune & Stratton, New York, 1958.*

Table 2.

Drugs Used in Myasthenia Gravis

Example of Generic Name	Brand Name
Azathioprine	Imuran
Cyclosporine	Sandimmune
Edrophonium	Tensilon
Neostigmine	Prostigmin
Prednisone	Meticorten
Pyridostigmine	Mestinon
Spirolactone	Aldactone
Cyclophosphamide	Cytosan
Mercaptopurine	Purinethol
Methotrexate	Mexate