MYASTHENIA GRAVIS
FOUNDATION OF AMERICA, INC.

Medications and Myasthenia Gravis

(A Reference for Health Care Professionals)

Robert M. Pascuzzi, MD Professor and Chairman
Department of Neurology Indiana University School of Medicine

Correspondence:
Robert M. Pascuzzi, MD
Department of Neurology
Emerson Hall 125
545 Barnhill Drive
Indiana University School of Medicine
Indianapolis, IN 46202 USA
Telephone: 317/274-4455
E-mail: rpascuzz@iupui.edu

Prepared by the Professional and Public Information Committee

Myasthenia Gravis Foundation of America
October, 2000

Most recent revision January 2007

Introduction

Patients with myasthenia gravis (MG) or Lambert-Eaton syndrome (LES) may have worsening of symptoms upon exposure to a variety of medications. Underlying disorders of neuromuscular transmission may affect presynaptic release of acetylcholine (LES) or the postsynaptic muscle fiber membrane at the endplate (MG). Similarly, adverse drug effects can occur presynaptically or postsynaptically. In a patient with a reduced safety factor for neuromuscular transmission, exposure to a drug or clinical state which further reduces the efficiency of neuromuscular transmission can result in significant clinical weakness.

Myasthenia Gravis

The prototype NMJ disease is myasthenia gravis (MG). Familiarity with this disorder assists the clinician in recognizing others involving defective neuromuscular transmission. Furthermore, since MG is the most common of the junctional diseases, it represents the most common clinical setting in which use of specific drugs may lead to clinical worsening. Myasthenia gravis is an autoimmune disorder of neuromuscular transmission involving the production of autoantibodies directed against the nicotinic AChR. Receptor antibodies are detectable in the sera of 80-90% of patients with MG. The prevalence of MG is about 1 in 10-20,000. Women are affected about twice as often as men. Symptoms may begin at virtually any age with a peak in women in the second and third decades, while the peak in men occurs in the fifth and sixth decades. Associated autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosis, and pernicious anemia are present in about 5% of patients. Thyroid disease occurs in about 10%, often in association with antithyroid antibodies. About 10-15% of MG patients have thymoma which is usually a benign tumor, and lymphoid hyperplasia with proliferation of germinal centers is present in 50-70% of patients.

Drug Induced (Iatrogenic) Autoimmune Myasthenia Gravis

There are three iatrogenic causes of autoimmune MG (D-penicillamine, interferon alpha, and bone marrow transplantation).

D-Penicillamine

D-Penicillamine is used to treat Wilson's disease, rheumatoid arthritis, other chronic autoimmune diseases, and cystinuria. Use of D-penicillamine has been associated with a variety of immune-mediated complications

including polymyositis, systemic lupus erythematosis, nephritis due to immune complex deposition, scleroderma, and pemphigus. Since the initial reports of penicillamine-related autoimmune MG by Bucknall et al. and Czlonkowska in 1975 over 100 such cases have been documented in the literature.[7,8] The symptoms in penicillamine-induced MG are usually mild and may be limited to extraocular muscles, including isolated ptosis.[9] Patients develop AChR antibodies, classic electromyographical abnormalities, and the typical improvement with use of cholinesterase inhibitors. Nerve-muscle preparation studies from intercostal muscle biopsies have shown reduced MEPP amplitude typical for acquired MG. Other than taking penicillamine, the patients are indistinguishable from those with idiopathic autoimmune MG.[10-16] The diagnosis can be easily missed, especially in patients presenting with respiratory failure.[17] Myasthenia is reported to occur in from 1% to 7% of all patients on penicillamine.[18,19] One group found MG in 5 out of 71 consecutive patients with penicillamine-treated rheumatoid arthritis within a two year period.[19] The frequency of MG from penicillamine therapy may be less for patients with Wilson's disease than those receiving the drug for treatment of rheumatoid arthritis, suggesting an underlying susceptibility to an immune-mediated process. One study of 60 patients with Wilson's disease who were treated for more than 6 months with penicillamine revealed none with clinical symptoms or examination evidence for MG and no decrement to repetitive stimulation (though some had low titers of acetylcholine receptor antibodies).[19a] Onset of MG symptoms typically occurs from two to twelve months following the initiation of penicillamine.[20] In general MG is less severe than idiopathic MG although some patients require mechanical ventilation. Discontinuation of penicillamine leads to complete resolution of MG symptoms in 2-6 months in the majority of patients. By one year MG symptoms have completely resolved in about 70% of patients, the titer of AChR antibodies improves, and the electrophysiological abnormalities improve or resolve.[20,21] The fact that some patients remain symptomatic long after stopping penicillamine suggests that in some cases, especially those with rheumatoid arthritis or other underlying autoimmune disease, MG may have been present subclinically prior to treatment with penicillamine and simply exacerbated by exposure to the drug. The management of MG involves discontinuation of penicillamine, and the use of conventional treatments available for the treatment of autoimmune MG.

The mechanism for penicillamine induced MG is unclear.[22] Studies of penicillamine reaction with purified AChR from Torpedo California show covalent attachment to two receptor subunits, alpha and gamma, presumed to result from reduction and formation of mixed disulfides.[12] Penicillamine modifies the equilibrium of ACh binding properties of both purified receptor and receptor rich membrane fragments.[12] Penicillamine given to normal rats in doses equivalent to human therapy results in no acute neuromuscular abnormalities.[23] Prolonged administration to guinea pigs in high doses results in a mild degree of neuromuscular block.[24] Therefore, there is little evidence to suggest that the drug has a direct effect on neuromuscular transmission. The latency to onset of symptoms and the presence of AChR antibodies indicate that the drug induces the autoimmune attack. Reduced sulphoxidation capacity observed in 8 of 9 patients with penicillamine-induced MG suggests that poor sulphoxidation may predispose the patient to developing MG.[25] Other drugs with similarities to penicillamine also used in the treatment of rheumatoid arthritis include tiopronin and pyrithioxin. An occasional association with MG has been reported with both drugs.[26,27]

Interferon Alpha

Patients treated with interferon alpha develop a variety of autoantibodies and autoimmune diseases. The initial reports of interferon induced MG occurred in 1995 when a 66 year old man was reported having developed sero-positive generalized MG about 6 months after starting interferon alpha therapy for leukemia.[28] Subsequently, MG has developed in other patients during interferon alpha-2b treatment for malignancy.[29,30] Patients treated for chronic active hepatitis C with interferon alpha have also developed autoimmune MG with onset from 6-9 months after starting treatment. In one case MG symptoms persisted for at least 7 months after stopping the drug.[31,32] Fulminate myasthenic crisis may occur after interferon alpha therapy.[33]

Regarding the mechanism of interferon-induced MG; the expression of interferon gamma at motor endplates of transgenic mice results in generalized weakness, abnormal NMJ function, and improvement with cholinesterase inhibitors. Immunoprecipitation analysis indicates that a previously unidentified 87-kD target antigen is recognized by sera from those transgenic mice and also from human MG patients. Such studies suggest that the expression of interferon gamma at motor endplates in these transgenic mice provokes an autoimmune humoral response, similar to that which occurs in human MG.[34] While the number of anecdotal case reports has increased

to suggest a cause and effect relationship between interferon alpha and MG,[34a,34b,34c,34d,34e,34f] recent reports have also suggested that MG may occur independently in association with hepatitis C.[34g,34h]

Interferon beta has been noted in several multiple sclerosis patients to be associated with the development of MG symptoms 9 to 12 months after the initiation of treatment.[34i, 34j]

Bone Marrow Transplantation

The third iatrogenic cause for autoimmune MG is bone marrow transplantation (BMT), first reported in 1983 in association with thymoma and antiskeletal muscle antibodies.[35,36] Myasthenia occurs as one manifestation of the graft versus host disease (GVHD).[37,38] Acute GVHD immediately after BMT is generally not associated with neurological manifestations. In contrast, chronic GVHD is associated with several neurological problems including polymyositis and MG.[39] Some patients develop both of these neuromuscular disorders rendering the diagnosis difficult. MG seems more likely to occur in patients treated with BMT for aplastic anemia, some of whom have shown AChR antibodies prior to transplantation. In BMT-associated MG the clinical features are classic for autoimmune MG; AChR antibodies are present, symptoms respond to CEI, and improve with immunosuppressive therapy.[40,41] The onset of MG tends to be delayed from several months to as long as 10 years after BMT.[42,43,39] Myasthenia is a relatively uncommon neurological complication of BMT. In one series of 6 children having neuromuscular complications of allogenic BMT only one had MG while four had myositis, and one had chronic inflammatory demyelinating polyneuropathy.[44] Patients respond to CEI and immunosuppressive therapy typical for autoimmune MG.

Metabolic Impairment of Neuromuscular Transmission

Magnesium and Hypermagnesemia

Hypermagnesemia is an uncommon clinical situation associated with the use of magnesium-containing drugs.[45] Magnesium (Mg++)is contained in some antacids and laxatives. Magnesium sulfate (MgSO4) is used in the treatment of preeclampsia/eclampsia, for hemodynamic control during anesthesia and the early postoperative period[46], and in patients depleted of Mg++ (such as chronic alcoholism). Normal serum magnesium runs 1.5 to 2.5 mEq/l (2 to 3 mg/dl) which is stabilized through exchange with tissue stores in bone, liver, muscle, and brain; also, serum Mg++ concentration is maintained via renal excretion. Patients having renal failure are

predisposed to developing hypermagnesemia, and should avoid magnesium-containing antacids and laxatives for this reason.[47,48] Elevated serum magnesium levels due to oral use of magnesium-containing compounds is very uncommon, so long as the patient has normal renal function.[49,50] Hypermagnesemia is occasionally seen with use of enemas, but usually in patients with an underlying GI tract disorder.[49,51] In the treatment of pre-eclampsia hypermagnesemia occurs commonly due to administration of high doses of parenteral MgSO4, at times resulting in serious side effects in the mother or the newborn.[52-54] The clinical features of hypermagnesemia correlate fairly well with the serum magnesium levels.[49,55,56] In treating pre-eclampsia, the neuromuscular transmission effects are monitored and used as a limiting factor in dosage. With serum levels above 5 mEq/l, the muscle stretch reflexes become reduced, while levels of 9 to 10 mEq/l are associated with absent reflexes and clinically significant weakness. In treating pre-eclampsia, muscle stretch reflexes are tested serially, and magnesium administration is stopped if the reflexes disappear.[53] Serum levels between 3.5 and 7 mEq/l are usually associated with no significant adverse effects in pre-eclamptic women, but clinical weakness is common with levels greater than 10 mEq/l and death from respiratory failure can occur.[52,53] Serum levels above 14 mEq/l can induce acute cardiac arrhythmia including heart block and arrest. Additional symptoms from autonomic nervous system involvement include dry mouth, dilated pupils, urinary retention, hypotension, and flushing skin thought to be from presynaptic blockade at autonomic ganglia.[57] Although patients can develop severe weakness, mental status is usually not directly affected.[56] Extraocular muscles tend to be spared. Reduced level of consciousness may occur indirectly as a result of hypoxia, hypercarbia or hypotension.

Magnesium interferes with neuromuscular transmission by inhibiting release of ACh.[58] Magnesium competitively blocks calcium entry at the motor nerve terminal. There may also be a milder postsynaptic affect. Clinically, hypermagnesemia resembles Lambert-Eaton syndrome more so than autoimmune MG.[59] In addition, magnesium can potentiate the action of neuromuscular blocking agents, which has been emphasized in women who had cesarean section after treatment with Mg++ for preeclampsia.[60,61] Patients with underlying junctional disorders are more sensitive to Mg++-induced weakness. Patients with MG[62,-64] and Lambert-Eaton syndrome[65,66] have been reported to exacerbate in the setting of Mg++ use in spite of normal or only mildly elevated serum levels. Typically, increased MG symptoms occur with parenteral magnesium administration, but

on occasion is seen with oral use.[66] Therefore, parenteral Mg++ administration should be avoided and oral Mg++ preparations used with caution in patients with known junctional disease (myasthenia gravis, Lambert Eaton syndrome, botulism, etc.).

The effects of standard parenteral doses of MgS04 on neuromuscular transmission of pre-eclampsia or preterm labor patients are significant, though largely subclinical. Train-of-four (TOF) recordings obtained from the thenar muscles before and 30 minutes after MgSO4 infusion shows an increase in tension of the contractile response in the control or baseline recordings, but the post infusion TOF shows no increase, but rather "fade' of the response.[67] These data suggest that in this patient population clinically relevant infusions of MgSO4 produced significant changes in neuromuscular transmission as manifested by loss of the treppe phenomenon and diminished TOF response.[67]

MgSO4 60mg/kg effects on residual neuromuscular block after administration of vecuronium is also significant.[46] Patients given Mg++ immediately upon recovery from vecuronium block or one hour later demonstrate rapid and profound recurarization as measured by electromyography and TOF studies.

Treatment of the hypermagnesemic patient depends on the severity of clinical symptoms. Discontinuation of magnesium is the first step; if the patient is significantly weak, administration of intravenous calcium gluconate 1 gram over three minutes can produce rapid, although temporary improvement (so long as the patient has normal renal function typical for a patient being treated for pre-eclampsia). If hypermagnesemia is more severe or if there are life threatening side effects such as cardiac arrhythmia or renal failure, hemodialysis is indicated.[68] If patients have MG or Lambert Eaton syndrome, they will respond poorly to calcium. Such patients may respond better to CEI.[63]

Other Electrolyte Disorders

Weakness from hypokalemia is believed to result from decreased excitability of muscle cell membranes.[69] Hypokalemia is implicated as a potential factor in worsening MG symptoms, especially in the setting of corticosteroid therapy, but the relationship has received only limited study.[70] Diuretics may aggravate MG weakness, possibly by depleting potassium.[71] In spite of the crucial role of intracellular calcium concentration in

ACh release little data exist on the effects of hypocalcemia on neuromuscular transmission. While hypocalcemia is well known to result in peripheral nerve hyperexcitability, tetany and convulsive seizures, there is no clear establishment of a clinically significant effect on neuromuscular transmission.[45] Clinical decompensation of MG patients during plasma exchange, ostensibly from citrate used in the intravenous replacement fluids, is suggested to be mediated by citrate induced hypocalcemia.[72]

Botulinum Toxin

As botulinum toxin A has become increasingly utilized to treat focal dystonia and spasticity, it has become apparent that there is potential for symptomatic complications from excess toxin. Botulinum toxin blocks ACh release at the presynaptic motor nerve terminal (and causes dysautonomia by blocking muscarinic autonomic cholinergic function as well). The intracellular target of botulinum toxin appears to be a protein of the ACh vesicle membrane. The toxin is a zinc-dependent protease which cleaves protein components of the neuroexocytosis apparatus.[73-75] Not only is its' effect local at the site of injection into muscle, but there is some degree of distant effect as well.[76] Dysphagia is a frequent side effect of botulinum injection for spasmodic dysphonia, typically lasting for about two weeks.[77] On occasion the dysphagia is severe, especially when patients report some degree of pretreatment dysphagia.[77] Prospective study of complications of botulinum toxin injections for cervical dystonia showed that prior to treatment 11% of patients had symptoms of dysphagia while 22% had radiologic evidence for abnormal peristalsis.[78] After injections of botulinum toxin new symptoms of dysphagia developed in an additional 33% of patients (those with pretreatment dysphagia were unchanged) and 50% developed new peristaltic abnormalities by radiographic study.[78] Single fiber EMG of the forearm muscle following treatment of cervical dystonia and hemifacial spasm show abnormal increase in mean jitter (suggesting impaired neuromuscular transmission) and six weeks after treatment there is increased fiber density indicating reinnervation.[79] In addition, mils abnormalities of cardiovascular reflexes suggest distant effects on autonomic function.[79] Previously undetected Lambert-Eaton syndrome has been unmasked in a patient following local botulinum toxin injection.[80] Myasthenic crisis has been reported following injections of botulism toxin.[80a] Clearly, botulinum toxin is relatively contraindicated in patients with a known defect of neuromuscular transmission. In addition, the clinician should be alert to the development of excessive weakness in the region of

local injection, or even remote sites, particularly with higher doses of botulinum toxin. Several excellent recent reviews of botulism are included in the reference list.[80b, 80c]

Drugs Used in Anesthesiology

General Anesthetics

Patients with underlying junctional disease such as MG are well known for the propensity towards prolonged weakness following anesthesia for surgical procedures. The cause for such potential difficulty is likely to be multifactorial. General anesthetics may potentiate neuromuscular blocking drugs in myasthenic patients. In addition, the inhalation anesthetics may have a direct effect on neuromuscular transmission. The routine administration of the inhalant anesthetic methoxyflurane is reported to unmask mild MG.[82] With repeated exposure the patient developed fatigue, weakness and ptosis for several hours, which improved after CEI. In experimental studies some inhalation anesthetics appear to alter post-junctional sensitivity to ACh, affect ionic conductance, and induce shortening of ACh-activated channel open time.[83]

Local Anesthetics

In a normal person local anesthetic use is unlikely to cause significant neuromuscular weakness. Intravenous lidocaine, procaine, and other local anesthetic agents can potentiate the effect of neuromuscular blocking drugs. There appear to be both presynaptic and postsynaptic effects. Interference with propagation of the nerve action potential at the nerve terminal and reduced ACh release may account for the presynaptic effects. [84] Local anesthetics also lead to reduced sensitivity of the postjunctional membrane to acetylcholine.[85] Harvey observed procaine to induce acute myasthenic crisis in 1939, but subsequent studies provide evidence to the contrary.[86,87]

Neuromuscular Blocking Drugs

Depolarizing and nondepolarizing neuromuscular blockers affect the muscle membrane potential. Neuromuscular blocking drugs may be modified by the degree of neuromuscular block, the associated disease state, acid base status of the patient, and associated electrolyte imbalance. In patients with MG and Lambert Eaton syndrome relatively small amounts of nondepolarizing agents can produce profound and prolonged NMJ blockade. Prolonged paralysis from neuromuscular blockers may occur on occasion in patients without NMJ disease. Factors which may influence the duration of neuromuscular blockade include dosage and duration of therapy, concurrent drug use (including muscle relaxants, magnesium, and cimetidine), severity of underlying

disease, electrolyte abnormalities, and renal insufficiency (which may lead to high drug concentrations).[88] Use of muscle relaxants for one week in a child resulted in a six week course of recovery.[89] Similarly, long-term weakness from vecuronium use is reported to occur in adults.[90,91] Paralysis lasted eight weeks after use of the neuromuscular blocker atracurium besilate.[92] Patients with metabolic acidosis, high serum magnesium levels, renal failure, and high blood levels of 3-desacetyl-vecuronium appear more likely to experience prolonged paralysis.[93] Prolonged neuromuscular blockade can be severe enough to produce neurogenic muscle atrophy.[94] Corticosteroids may even potentiate the effects of muscle relaxants.[95] Prolonged weakness in intensive care patients can result from a multitude of causes, some leading to peripheral neuropathy and myopathy as well as junctional disturbance as above. In many patients there are multiple concomitant factors leading to the paralytic picture.[96,97]

Depolarizing agents, including succinylcholine, should be used with caution in patients with known NMJ disease. The inhibition of hydrolysis by cholinesterase inhibitors will result in prolonged duration of action. Patients with MG are less sensitive to this drug than the nondepolarizing agents. Occasionally, patients with MG have their disease unmasked by the use of these drugs. Pharmacological effects of neuromuscular blockers are influenced by antibiotics, general anesthetics, local anesthetics, and antiarrhythmics which may complicate clinical weakness. Newer neuromuscular blocking agents having shorter duration of action may still aggravate MG and Lambert-Eaton syndrome weakness. Occasional reports of reduced plasma cholinesterase levels by plasma exchange or by genetic abnormalities have been associated with reports of prolonged apnea and muscle weakness in patients receiving depolarizing neuromuscular blocking drugs.

Agents That Impair Neuromuscular Transmission and May Increase Weakness in Patients with Underlying Junctional Disorders

Antibiotics

In 1941 Robinson and Molitor showed that tyrothricin (gramicidin) could produce respiratory failure in animals.[98] In 1956 Pridgen reported respiratory arrest as a result of intraperitoneal neomycin in humans.[99] He noted four patients without prior neuromuscular symptoms who developed apnea from intraperitoneal neomycin sulfate, two of whom died. Subsequently, numerous case reports of neuromuscular weakness from antibiotic administration thought to be a result of impaired neuromuscular transmission have been reported in

normal patients, those concurrently receiving neuromuscular blocking drugs, those with MG, those with other disorders that might alter pharmacokinetics, and patients with exposure to other drugs having an adverse effect on neuromuscular transmission.[100-105]

The aminoglycoside antibiotics are well established to impair neuromuscular transmission and produce clinically significant weakness, regardless of the method of administration.[103] Weakness appears to be dose-dependent and reflected by serum levels. Cholinesterase inhibitors, infusion of calcium, and aminopyridines can partially reverse the weakness produced by aminoglycosides.[106-108] Microelectrode studies on nerve muscle preparations suggest that the effect is presynaptic, postsynaptic or both, and may depend on the specific aminoglycoside. Tobramycin appears to have predominantly presynaptic effects similar to hypermagnesemia with impairment of ACh release.[109-111] In contrast, netilmicin acts postsynaptically by blocking the binding of ACh to receptors, as is caused by curare.[109-111] Of the studies of amikacin,[112] gentamicin,[113] kanamycin,[114] neomycin,[115] netilmicin, streptomycin[116] and tobramycin,[117] neomycin appears to be the most potent in interfering with neuromuscular transmission, while tobramycin would appear to be the least toxic in this regard.[109]

Gentamicin, neomycin, streptomycin, tobramycin and kanamycin have been reported to produce clinically significant muscle weakness on occasion in non-MG patients.[4] Patients with infantile botulism and MG can also have increased weakness upon exposure to these antibiotics.[118-120]

Other antibiotics including tetracyclines, sulfonamides, penicillins, amino acid antibiotics, nitrofurantoin[120a] have either been associated with occasional anecdotal reports of increased myasthenic weakness or implicated from in vitro studies to be potentially problematic. Fluoroquinolones have also been associated with anecdotal reports of increased weakness in myasthenic patients or implicated from *in vitro* studies to adversely affect neuromuscular transmission. Acute worsening of MG has been reported following administration of ciprofloxacin, a fluroroquinolone.[121,121a,121b] Exacerbation of MG has been reported with use of perfloxacin, ofloxacin, and also norfloxacin.[122,123,123a]

Clindamycin and lincomycin are monobasic amino acid antibiotics which differ from aminoglycosides.[124,125] The neuromuscular blockade produced by these drugs is not readily reversed with CEI. These drugs have pre- and postsynaptic affects by microelectrode studies with reduced MEPP frequency, reduced evoked transmitter release, and reduced sensitivity of the postjunctional AChR.[126,127] Junctional effects of lincomycin can be reversed with increased calcium concentration or with use of aminopyridines.[128] However, CEI may aggravate the effect. Clindamycin may also directly block muscle contractility.[127] Vancomycin may potentiate the neuromuscular blockade of succinylcholine.[129]

Colistin, colistinmethate, and polymyxin B are reported to produce weakness, especially in patients with renal insufficiency and when used in combination with other neuromuscular blocking drugs or antibiotics.[130-135] Their mechanism of action includes reduced ACh release and, to some degree, postsynaptic blockade of the receptor.[136-138] Acute respiratory failure in MG may occur following a single intramuscular injection of colistimethate.[139] Colistin has been reported to cause acute weakness in patients with underlying MG.[140]

While tetracycline has not been associated with weakness or abnormal *in vitro* abnormalities, several analogs of tetracycline, including rolitetracycline and oxytetracycline, are reported to exacerbate MG weakness. The mechanism for this effect is not known. Some studies show no deleterious effect of tetracycline.[141,109]

Ampicillin is rarely reported to increase weakness of MG patients and increase the percent of decremental response on repetitive stimulation in rabbits with experimental MG.[142] Ampicillin also can lead to single fiber EMG abnormalities.[143] In vitro studies on nerve-muscle preparations have not shown clear cut abnormalities to indicate if the effect is presynaptic or postsynaptic.[142]

Myasthenic patients occasionally report increased weakness with erythromycin and physiological studies in normal humans suggest it has a presynaptic effect.[3,144] Severe exacerbation of MG has been reported beginning one hour after taking 500mg azithromycin (Zithromax), an azalid-antibiotic of the macrolid group. The patient required mechanical ventilation for six days. The same patient had previously had a similar exacerbation after taking another macrolid, erythromycin. Therefore, these antibiotics should also be used with caution in patients with MG.[145]

Telithromycin (Ketek), a new ketolide antibiotic is a semi-synthetic substance derived from erythromycin . It belongs to the family of ketolides, closely related to macrolide antibiotics. Telithromycins's primary indication has been for the treatment of serious respiratory infections (such as bacterial pneumonia). It has been used in Europe since 2001 and in the US following the FDA's approval in 2004. Telithromycin has been implicated in the exacerbation or unmasking of myasthenia gravis. [145a,145b] In a report from 2006 analyzing 10 MG patients from France with exacerbation of symptoms in the setting of telithromycin treatment the onset of symptoms in 7of 10 patients was within 2 hours of the first dose and exacerbations were observed in some cases to be severe and life-threatening.[145c]. Based on these observations telithromycin is not generally recommended for use in patients with myasthenia gravis (and if physicians determine that there are no other therapeutic alternatives in a critically ill patient then such patients must be closely monitored for increasing myasthenic weakness).

Clearly the issue of antibiotic effects on neuromuscular transmission is complex and poses a vexing dilemma for the clinician. Nearly every antibiotic ever studied has demonstrated some deleterious effect or has been the subject of a clinical report suggesting exacerbation of MG. If a patient requires antibiotic treatment for an infection then the appropriate drugs should be utilized. When managing patients with junctional disease it simply behooves the clinician to remain alert to the potential for clinically significant adverse effects, especially if the patient becomes weaker in the setting of antibiotic use.

Cardiovascular Drugs

Quinidine and Quinine

Quinidine and its stereoisomer quinine can aggravate weakness in MG.[146] A number of reports suggest that the quinidine can unmask previously undiagnosed or asymptomatic MG.[147-149] The drug acts presynaptically to impair the formation or release of ACh. In large doses it may also have a postsynaptic effect with a curare-like action. A number of references in the literature suggest that quinine can also aggravate myasthenic weakness. Quinidine has been observed to potentiate weakness induced by nondepolarizing and depolarizing neuromuscular blocking drugs.[150,151] Quinine has been used as a diagnostic test for MG in the past. Harvey and Whitehill in 1937 reported the differential affects of quinine and prostigmine in the diagnostic evaluation of

MG.[152] Similarly, Eaton in 1943 pointed out the diagnostic usefulness of trials of prostigmine and alternatively, quinine.[153]

Sieb et al. studied the effects of quinolone derivatives quinine, quinidine, and chloroquine on neuromuscular transmission using conventional microelectrode and patch-clamp techniques.[154] All three derivatives reduce quantal content of the endplate potential by 37-45% , and decrease the amplitude and decay time constant of the MEPP and miniature end-plate current. At progressively larger concentrations the MEPP becomes undetectable. The effect on MEPP is not reversed by neostigmine. Single-channel patch-clamp analysis of quinine effects reveal a long-lived open-channel and a closed-channel block of AChR. Tests for competitive inhibition or desensitization of the AChR by quinine in these concentrations are negative. Quinolone drugs adversely affect both presynaptic and postsynaptic aspects of neuromuscular transmission at concentrations close to those employed in clinical practice. Therefore they should not be used, or used only with extreme caution, in disorders having a reduced safety margin of neuromuscular transmission.[154] I have cared for patients whose MG decompensated in the setting of quinine 325mg qhs for treatment of leg cramps. In both cases the patients developed markedly increased weakness within hours to days of starting the medication. Anecdotal reports suggest that consumption of tonic water containing small amounts of quinine can result in exacerbation of myasthenic symptoms.

Beta Blockers

Beta adrenergic blocking drugs have been observed on occasion to be associated with increasing weakness in MG patients including propranolol, oxprenolol, timolol, and practolol.[155-159] While beta blockers are unlikely to produce frank muscle weakness in normal patients, they are notorious for inducing subjective fatigue. Furthermore, occasional patients describe transient diplopia in the setting of beta blocker usage to raise the question of a NMJ mechanism in such patients.[160] *In vitro* microelectrode studies of nerve-muscle preparations reveal that atenolol, labetelol, metoprolol, nadolol , propranolol, and timolol all produced dose-dependent reduction in neuromuscular transmission in rat skeletal muscle.[161,162] Both presynaptic and postsynaptic affects have been observed. Reduced MEPP amplitude can be caused by any of the beta blockers, suggesting a postsynaptic site of action. Presynaptic abnormalities include reduced MEPP frequency, and with metoprolol

and propranolol there is reduced quantal content. Propranolol seems to have the most marked effect impairing neuromuscular transmission with atenolol having the least.[161,162] The specific mechanism for the beta blocker junctional effect is unclear.

In 10 patients with mild to moderate MG who received intravenous propranolol 0.1 mg/kg at 1 mg/minute there was no detectable effect on the decrement to repetitive nerve stimulation or on "clinical tests", leading the investigators to conclude "there is no rapid deterioration of neuromuscular transmission in patients with moderately severe MG after injections with therapeutic doses of propranolol....".[163] Such findings are consistent with my own observations in practice - the use of beta blockers in MG patients is unlikely to cause significant worsening of their symptoms.

Calcium Channel Blockers

A variety of observations indicate that calcium channel blockers may adversely affect neuromuscular transmission.[171a] Presynaptic reduction in ACh release and also postsynaptic curare-like effects have been observed in experimental settings.[164-166] Calcium channel blockers can potentiate the effect of neuromuscular blocking drugs.[167,168] Verapamil has been associated with increased weakness and respiratory failure with intravenous use in a patient with Duchenne dystrophy.[169] A patient with Lambert-Eaton syndrome exacerbated after receiving verapamil.[170] Verapamil is implicated as the cause for respiratory failure in a patient with MG.[3] Jonker's group prospectively studied the effects of intravenous administration of verapamil on decrement to repetitive nerve stimulation and clinical function in 10 patients with mild to moderate myasthenia gravis. Verapamil doses of 0.1 mg/kg given at a rate of at 1 mg/minute showed no adverse effects on neuromuscular transmission.[163]

Protti et al. studied the effect of calcium channel blockers on transmitter release at normal human neuromuscular junction, observing that P-type calcium channel blockers blocked nerve evoked muscle action potentials and inhibited evoked synaptic transmission.[171] But transmitter release was not affected either by nitrendipine, an L-type channel blocker, or omega-Conotoxin-GVIA, an N-type channel blocker. Those observations suggest that P-type channels mediate transmitter release at the motor nerve terminals.

Procainamide can lead to acute worsening of MG. Although the drug can induce autoimmune phenomena, the immediate onset of weakness and neuromuscular blockade would suggest a direct effect on neuromuscular transmission, as opposed to an indirect autoimmune process.[172,173] Procainamide appears to act presynaptically in reducing formation of ACh or inhibiting its release, and there is some evidence to implicate postsynaptic factors as well. Bretylium may induce muscle weakness as well as potentiate the effect of neuromuscular blockers.[174] Trimethaphan is a ganglionic blocking agent used occasionally for treating extreme hypertensive emergency and other acute vascular emergencies. It has been associated with acute neuromuscular weakness, including respiratory failure, and there is speculation that it has a curare-like action at the neuromuscular junction. In addition, the drug can potentiate neuromuscular blockade in patients receiving nondepolarizing and depolarizing neuromuscular blocking drugs.[175-178]

Statins: Lipid-lowering Drugs

Statin drugs have been in wide usage for many years and in the setting of thousands of patient-years experience there have been a small number of reports of myasthenic weakness temporally-associated with their use. It is unclear whether these patients represent statin-induced MG or aggravated of mild or sub-clinical disease.178a,178b,178c,178d Of 6 patients in the literature all developed symptoms of MG, 4 of 6 had acetylcholine receptor antibodies, 5 of 6 patients started experiencing MG symptoms within 2 weeks of initiating statin treatment (and one at 3 months). In 5 of the 6 patients the symptoms resolved following discontinuation of statin therapy.

Antiepileptic Drugs

Phenytoin has demonstrated presynaptic and postsynaptic affects on neuromuscular transmission invitro.[179,180] Occasional patients with MG have presented following treatment with phenytoin,[180,181] mephenytoin , and trimethadione.[182,183] In some of these cases the weakness has resolved following discontinuation of the anticonvulsant. In vitro studies of nerve-muscle preparations have shown that phenytoin reduces quantal release of acetylcholine from the motor nerve terminal; also, it produces a simultaneous increase in spontaneous release of neurotransmitter (and therefore increases the MEPP frequency). One explanation for this effect is a reduction in the size of the nerve action potential at the motor nerve terminal, or perhaps a reduction in calcium influx

into the motor nerve terminal. Postsynaptic effects have also been observed with phenytoin including reduction in the MEPP amplitude (thought to be related to desensitization of the endplate).[184] Osserman and Genkins observed that barbiturates can aggravate MG weakness.[185] In vitro studies suggest that barbiturates and ethosuxamide produce postsynaptic neuromuscular blockade, while carbamazepine has an effect on presynaptic junctional function.[186,187] Trimethadione can induce a variety of autoimmune complications including systemic lupus and nephrotic syndrome.[188] Weakness in the setting of trimethadione has been associated with autoantibodies against skeletal muscle, nuclear antigens and thymus, and has gradually resolved following removal of the drug.[182,183]

Recent reports have included the observation of seropositive myasthenia gravis occurring after three months of gabapentin therapy for painful neuropathy.[188a] Following withdrawal of the drug, the patient became asymptomatic, although serologic studies remained abnormal. The same authors followed up their clinical experience with an evaluation of gabapentin in rats with experimental autoimmune myasthenia gravis, noting an abnormal decremental response to 3 Hz repetitive stimulation, transiently, following the exposure to gabapentin, while no decrement was observed in normal rats. The authors rightfully conclude that the drug should be used with some caution in myasthenia gravis. The point is of particular importance in myasthenics who have muscle cramps. Such patients should avoid quinine, and it has been a common practice to prescribe gabapentin for control of muscle cramps.

Another recent report emphasized the presence of a defect of neuromuscular transmission as demonstrated by a decremental response at high frequency repetitive stimulation in children who had received an overdose of carbamezapine.[188b] Additional question of association of MG symptoms and use of carbamazepine in children has been questioned.[188c]

Further study of antiepileptic drugs is needed before sweeping guidelines can be made regarding their use in patients with junctional disease. In my judgment the overall risk of using anticonvulsants in MG patients is small.

Analgesics

Narcotic analgesics do not directly interfere with neuromuscular transmission in myasthenia.[189,190] There may be an indirect effect on the myasthenic patient, however. Slaughter in 1950 demonstrated that cholinesterase inhibitors (neostigmine) may potentiate the effects of morphine, codeine, hydromorphone, and opium alkaloids.[191] Grob reported sudden death abruptly after administration of morphine sulfate.[192] Due to the tendency of narcotic analgesics to produce respiratory depression, they should be used with caution in patients who have respiratory insufficiency from myasthenia gravis or other neuromuscular diseases.

Hormonal Medications

Corticosteroids

About 50% of patients with MG receiving treatment with high-dose corticosteroids have an early exacerbation; in about 10% this exacerbation is severe, requiring mechanical ventilation or a feeding tube.[193] The mechanism for this exacerbation is unclear. Using a lower starting dose of corticosteroids, with a gradual increase over time, may reduce the risk of early exacerbation.[194] In experimental neuromuscular preparations there appears to be some direct affect on neuromuscular transmission including depolarization of nerve terminals, reduced ACh release, altered MEPPs, alteration of choline transport, and intracellular potassium depletion - some of which may be clinically significant mechanisms of action.[195-198]

Alternatively, the effect may be immune-mediated. Abramsky et al. found increased lymphocyte transformation *in vitro* in patients with prednisone-induced aggravation of weakness.[199] Nonreactive lymphocytes may be destroyed by corticosteroids, leading to enhanced proliferation of sensitized lymphocytes.[199-201]

Estrogen

Although poorly understood, it is commonly believed among neuromuscular clinicians that MG may fluctuate with the menstrual cycle and pregnancy, suggesting an influence of estrogen or progesterone on neuromuscular transmission, the immune system or some other aspect of MG. On occasion estrogen therapy has been associated with increasing weakness in MG, including parenteral use after 3 to 5 days.[202-203] An isolated case occurred in a woman taking birth control pills.[204] Another patient experienced the onset of MG about four months following implant of levonorgestrel (Norplant).[205] Symptoms progressed over the next nine months, and

AChR antibodies were present. Within one week of removal of the implant her symptoms markedly improved.[205]

Thyroid Imbalance

Hyperthyroidism and hypothyroidism can be associated with increasing myasthenic weakness.[206,207] The mechanism is unclear. Any patient with underlying MG who develops progressive weakness should be screened for abnormal thyroid function unless there is an obvious alternative explanation.

Ophthalmologic Medications

Timolol, the beta adrenergic blocking eye drop, has been reported to be associated with increased myasthenic weakness.[157,159] Similar observations have been made with betaxolol hydrochloride.[208] Echothiophate is a long-acting cholinesterase inhibitor used in the treatment of open angle glaucoma, and has been reported to be associated with muscle weakness and fatigue; temporally related to the use of the medication, resolving when the medication is stopped.[209] The mechanism of weakness is not clear but might relate to long-acting cholinesterase inhibitor-induced cholinergic weakness.

Psychiatric Drugs

Phenothiazines

Chlorpromazine was reported to produce increased muscle weakness in a schizophrenic patient with MG by McQuillen in 1963.[210] In vitro studies have demonstrated a postsynaptic effect with reduced MEPP and EPP amplitudes without change in quantal content or MEPP frequency.[211] Still other studies have implicated a presynaptic site. Chlorpromazine and promazine can antagonize applied ACh, and may prolong effects of succinylcholine. Occasional reports note that in patients receiving chlorpromazine or phenelzine, subsequent administration of depolarizing neuromuscular blocking drugs results in prolonged neuromuscular blockade.

Lithium

Subjective weakness is a common side effect of lithium carbonate. Exacerbation or unmasking of MG is reported.[212,212a] Lithium can prolong the effect of neuromuscular blockers.[213-214] The mechanism for the lithium-induced junctional effect may result from its accumulation inside the presynaptic motor nerve terminal and becoming a competitive cation for calcium; thus, reducing ACh synthesis and voltage-gated quantal release of

ACh.[215] Other studies suggest that there is a reduced number of ACh receptors in denervated muscle preparations, raising the question that lithium may selectively increase the rate of breakdown of receptors without changing the rate of synthesis. The onset of weakness in a patient with MG can occur within days of starting lithium.

Amitriptyline, amphetamines, droperidol, haloperidol, imipramine, paraldehyde, and trichloroethanol have been found to impair neuromuscular transmission in experimental settings.[2,3]

Chloroquine

Chloroquine is widely used for treatment of malaria, but on occasion is used in the treatment of autoimmune connective tissue disorders including rheumatoid arthritis, discoid lupus, and even porphyria cutanea tarda. It has a variety of potential neurologic complications, including peripheral neuropathy and myopathy, as well as an effect on neuromuscular transmission. The mechanism of the chloroquine effect on neuromuscular transmission is controversial and may be multifactorial. Chloroquine appears to have a direct effect at the presynaptic level with reduced MEPP amplitude as well as having a postsynaptic effect with competitive postjunctional blockade.[154] Clinical support for the direct effect stems from observation of weakness developing within the first week after beginning chloroquine therapy, with absent AChR antibodies, and rapidly resolving symptoms upon drug withdrawal.[216] Chloroquine has been reported to directly reduce muscle membrane excitability. In addition, there is some belief that the drug may induce an autoimmune disorder similar to that triggered by D-penicillamine.[217,218] Several patients with autoimmune diseases (rheumatoid arthritis and SLE) developed clinical, physiologic, and pharmacological evidence for MG after prolonged use of chloroquine. These patients had AChR antibodies which eventually disappeared, as did the other abnormalities following discontinuation of the drug. In a review of twelve patients in which chloroquine exacerbated or unmasked MG about half were associated with long-term high-dose therapy while the remainder occurred in the setting of brief low-dose treatment for prevention of malaria.[219]

Iodinated Radiographic Contrast

Several studies have suggested that intravenous iodinated contrast can trigger or precipitate acute myasthenic worsening.[220-223] The initial reports of three patients in 1985 noted myasthenic crisis after administration of

intravenous iodinated contrast.[220, 221] These patients had abrupt apnea and several days of severe myasthenic weakness. The occurrence is controversial, and not uniformly observed.[224] Frank reported a similar patient but found the overall risk of a severe reaction in MG patients to be only about 2 to 3% of all MG iodinated contrast exposures. One patient with Lambert Eaton syndrome developed acute transient respiratory insufficiency following intravenous contrast infusion, speculated to be on the basis of acute hypocalcemia from calcium binding of the contrast agent, and resulting presynaptic blockade with reduced ACh release.[222] While iodinated contrast may have a direct effect on neuromuscular transmission, an indirect mechanism is also possible, as part of a more nonspecific allergic-type contrast reaction. On the other hand, since patients with an acute intravenous contrast reaction typically receive medications such as diphenhydramine, which have significant anticholinergic side effects, perhaps some of the increased weakness could result from drugs used to treat the acute contrast reaction.[225] In my own experience acute myasthenic deterioration has occurred in several patients receiving iodinated contrast during CT scanning of the chest (looking for thymoma). For that reason we routinely perform noncontrasted chest CT scan (or MR scan) when screening MG patients for thymoma. On the other hand radiographic contrast preparations have advanced in recent years and there is an absence of new reports of myasthenic neuro-worsening in the past decade. The role of modern-day radiographic contrast agents in patients with myasthenia deserves further study.

There is one report in the older literature of deterioration related to gadolinium contrast.[225a]

Miscellaneous Drugs

D-L-carnitine (but not L-carnitine) has been to be associated with increased weakness in MG patients undergoing dialysis.[226] The mechanism is not known but may relate to the affect caused by hemicholinium or a post-synaptic block by the accumulation of acylcarnitine esters.[227] Emetine, used as an amoebocide and also the active ingredient of ipecac, has been observed to produce acute neuromuscular weakness as a side effect.[228,229]

The following medications have also been the subject of reports suggesting a potential for aggravating MG weakness: intravenous sodium lactate,[5] tetanus antitoxin,[230]and trihexyphenydyl (Artane).[231] Cocaine use may cause acute exacerbation of MG.[232] A single patient with chronic lymphocytic leukemia developed idiopathic

thrombocytopenic purpura and myasthenia gravis after treatment with fludarabine. [231a] Cisplatin therapy has been reported in a single patient with thymoma to be temporally associated with mysthenic crisis. [232a]
A single patient was reported with myasthenia gravis, myositis, and insulin-dependent diabetes mellitus in the setting of high-dose interleukin-2 in a patient with renal cell cancer.[232b]

Laboratory studies of the following drugs have demonstrated an abnormal effect on neuromuscular transmission. Amantadine reduces post-junctional sensitivity to ACh by interacting with the AChR ion channel of the AChR.[233] Diphenhydramine can potentiate the neuromuscular block of barbiturates and neuromuscular blocking agents, and reduce the amount of neurotransmitter released from the motor nerve terminal.[225] The H2 receptor blocker roxatidine impairs neuromuscular transmission in rat sciatic nerve-gastrocnemius muscle preparation.[234] Ritonavir has been associated temporally with MG symptoms in one report.[236]

A patient with ALS treated with riluzole for three months developed new ptosis and diplopia.[235] The patient had physiological and serological findings pointing to autoimmune myasthenia gravis. Riluzole was stopped and the patient's clinical status improved, as well as improvement in the titer of AChR antibodies. While the patient may have had a coincidental chance association of ALS and autoimmune myasthenia gravis, the report is notable for several reasons. It is a perfect example of 50 years of literature which provides an anecdotal report observing an association between myasthenia gravis, worsening of symptoms, and temporally-related use of a particular drug.

A patient with multiple sclerosis developed symptoms of myasthenia gravis in the setting of treatment with glatiramer acetate. [235a]

As with most of the literature on adverse drug effects in myasthenia gravis, the individual case reports and anecdotal observations must be considered in a thoughtful manner. One cannot be overly dogmatic about assuming that a reported association in an occasional patient is anything more than a chance coincidence. It would be inappropriate to ban the use of all drugs ever reported to be associated with a flare-up of myasthenia in such patients, as there would be very few drugs left that myasthenics could take. In addition, many of the conditions such as ALS that might be treated with quinine or gabapentin would be expected to have weakness

and fatigue related to their primary disease (ALS) or a secondary effect of the disease such as hypoventilation, nutritional issues or the medications themselves. To detect drug-induced or drug-related myasthenia gravis in such patients can be very challenging. The best recommendation is to be alert to those drugs which have been reported in the literature to be associated with a development of or worsening of myasthenia gravis, and to be cautious in using such drugs in known myasthenics. One can safely say that many drugs can have an effect on neuromuscular transmission and, in occasional patients, appear to adversely effect their clinical status – particularly if they have a known underlying defect of neuromuscular transmission. It behooves the neurologist to consider the potential for increasing weakness in any patient receiving a new medication, even if it is not on a list of drugs reported to aggravate myasthenia gravis.

References

General Discussions of Adverse Drug Effects

1. Pascuzzi RM. Iatrogenic disorders of the neuromuscular junction. In: Iatrogenic Neurology. Jose Biller, Ed. Butterworth-Heinemann 1998;283-304.

2. Argov Z, Mastaglia FL. Disorders of neuromuscular transmission caused by drugs. N Engl J Med. 1979;30:409-413.

3. Howard JR. Adverse drug effects on neuromuscular transmission. Sem Neurol 1990;10:89-102.

4. Kaeser HE. Drug induced myasthenic syndrome. Acta Neurol Scand 1984;70(S100):39-47.

5. Wittbrodt ET. Drugs and myasthenia gravis: an update. Arch Intern Med 1997;157(4):399-408.

6. Barrons RW. Drug-induced neuromuscular blockade and myasthenia gravis. Pharmacotherapy 1997;17(6):1220-1232.

Penicillamine

7. Bucknall RC, Dixon A St J, Glick EN, Woodland J, Zutshi DW. Myasthenia gravis associated with penicillamine treatment for rheumatoid arthritis. Br Med J 1975;1:600-602.

8. Czlonkowska A. Myasthenia syndrome during penicillamine treatment. Br Med J 1975; 2:726.

9. Reynauld JP, Lee YS, Kornfeld P, Fries JF. Unilateral ptosis as an initial manifestation of D-penicillamine induced myasthenia gravis. J Rheumatol 1993;20:1592-1593.

10. Masters CL, Dawkins RL, Zilko PJ, Simpson JA, Leedman RJ. Penicillamine-associated myasthenia gravis, antiacetylcholine receptor and antistriational antibodies. Am J Med 1977;63:689-694.

11. Russell AS, Lindstrom JM. Penicillamine-induced myasthenia gravis associated with antibodies to acetylcholine receptor. Neurology 1978;28:847-849.

12. Bever CT Jr, Chang HW, Penn AS, Jaffe IA, Bock E. Penicillamine-induced myasthenia gravis: effects of penicillamine on acetylcholine receptor. Neurology 1982;32:1077-1082.

13. Vincent A, Newsom-Davis J, Martin V. Anti-acetylcholine receptor antibodies in D-penicillamine-associated myasthenia gravis. Letters to the Editor. Lancet 1978;1254.

14. Vincent A, Newsome-Davis J. Acetylcholine receptor antibody characteristics in myasthenia gravis. II. Patients with penicillamine-induced myasthenia or idiopathic myasthenia of recent onset. Clin Exp Immunol 1982;49:266-272.

15. Albers JW, Hodach RJ, Kimmel DW, Treacy WL. Penicillamine-associated myasthenia gravis. Neurology 1980;30:1246-1249.

16. Fawcett PR, McLachlan SM, Nicholson LV, Argov Z, Mastaglia FL. D-Penicillamine-associated myasthenia gravis: immunological and electrophysiological studies. Muscle & Nerve 1982;5:328-334.

17. Adleman HM, Winters PR, Mahan CS, Wallach PM. D-penicillamine-induced myasthenia gravis: diagnosis obscured by coexisting chronic obstructive pulmonary disease. J Med Sci 1995;309:191-193.

18. Cooperative Systematic Studies of Rheumatic Disease Group. Toxicity of longterm low dose D-penicillamine therapy in rheumatoid arthritis. J Rheumatol 1987;14:67-73.

19. Andonopoulos AP, Terzis E, Tsibri E, Papasteriades CA, Papetropoulos T. D-penicillamine induced myasthenia gravis in rheumatoid arthritis: an unpredictable common occurrence? Clin Rheumatol 1994;13:586-588.

19a. Komal Kumar RN. Patil SA. Taly AB. Nirmala M. Sinha S. Arunodaya GR. Effect of D-penicillamine on neuromuscular junction in patients with Wilson disease. Neurology 2004;63:935-6.

20. Drosos AA, Christou L, Galanopoulou V, Tzioufas AG, Tsiakou EK. D-penicillamine induced myasthenia gravis: clinical, serological and genetic findings. Clin Exp Rheumatol 1993;1:387-391.

21. Bruggemann W, Herath H, Ferbert A. Follow-up and immunologic findings in drug-induced myasthenia. Med Klin 1996;91:268-271.

22. Kuncl RW, Pestronk A, Drachman DB, Rechthand E. The pathophysiology of penicillamine-induced myasthenia gravis. Ann Neurol 1986;20:740-744.

23. Aldrich MS, Kim YI, Sanders DB. Effects of D-penicillamine on neuromuscular transmission in rats. Muscle & Nerve 1979;2:180-185.

24. Burres SA, Richman DP, Crayton JW, Arnason BGW. Penicillamine-induced myasthenic responses in the guinea pig. Muscle & Nerve 1979;2:186-190.

25. Seideman P, Ayesh R. Reduced sulphoxidation capacity in D-penicillamine induced myasthenia gravis. Clin Rheumatol 1994;13:435-437.

26. Menkes CJ, Job-Deslandre C, Bauer-Vinassac D, Rouillon A, Rousseau R. Myasthenie induite par la tiopronine au cours du traitement de la polyarthrite rhumatoide. La Presse Medicale 1988;17:1156-1157.

27. Kirjner M, LeBourges J, Camus JP. Myasthenie induite par ia pyrithioxine au cours du traitement d'une polyarthrite rhumatoide. LaNouvelle Presse Medicale 1980;9:3098.

Interferon Alpha

28. Perez A, Perella M, Pastor E, Cano M, Escudero J. Myasthenia gravis induced by alpha-interferon therapy. Am J Hematol 1995;49:365-366.

29. Batocchi AP, Evoli A, Servidei S, Palmisani MT, Apollo F, Tonali P. Myasthenia gravis during interferon alpha therapy. Neurology 1995;45:382-383.

30. Lensch E, Faust J, Nix WA, Wandel E. Myasthenia gravis after interferon alpha treatment. Muscle Nerve 1996;19:927-928.

31. Piccolo G, Franciotta D, Versino M, Alfonsi E, Lombardi M. Myasthenia gravis in a patient with chronic active hepatitis C during interferon-a treatment. Letters to the Editor. Journal of Neurol, Neurosurg, and Psych 1996;60:348.

32. Mase G, Zorzon M, Biasutti E, Vitrani B, Cazzato G, Urban F, Frezza M. Development of myasthenia gravis during interferon a treatment for anti-HCV positive chronic hepatitis. Journal of Neurol, Neurosurg and Psych 1996;60:348-349.

33. Konishi T. A case of myasthenia gravis which developed myasthenic crisis after alpha-interferon therapy for chronic hepatitis C. Rinsho Shinkeigaku 1996;36:980-985.

34. Gu D, Wogensen L, Calcutt N, Xia C, Zhu S, Merlie JP, Fox HS, Lindstrom J, Powell HC, Sarvetnick N. Myasthenia gravis-like syndrome induced by expression of interferon in the neuromuscular junction. J Exp Med 1995;547-557.

34a. Bora I, Larli, Bakar M, et al. Myasthenia gravis following IFN-alpha-2a treatment. European Neurology 1997;38(1):68.

34b. Uyama E, Fujiki N, Uchino M. Exacerbation of myasthenia gravis during interferon-alpha treatment (letter). Journal of the Neurological Sciences 1996;144(1-2):221-222.

34c. Gurtubay IG, Morales G, Arechaga O, et al. Development of myasthenia gravis after interferon alpha therapy. Electromyography and Clinical Neurophysiology 1999;39(2):75-78.

34d. Borgia G, Reynaud L, Gentile I, et al. Myasthenia gravis during low-dose IFN-alpha therapy for chronic hepatitis C. J Interferon Cytokine Res 2001;21:469–70.

34e. Weegink CJ, Chamuleau RA, Reesink HW, et al. Development of myasthenia gravis during treatment of chronic hepatitis C with interferon-alpha and ribavirin. J Gastroenterol 2001;36:723–4.

34f. Harada H, Tamaoka A, Kohno Y, et al. Exacerbation of myasthenia gravis in a patient after interferon [beta] treatment for chronic active hepatitis C. J Neurol Sci 1999;165:182

Interferon beta

34i. Blake G, Murphy S. Onset of myasthenia gravis in a patient with multiple sclerosis during interferon-1b treatment. Neurology 1997;49:1747–8.

34j. Dionisiotis J. Zoukos Y. Thomaides T. Development of myasthenia gravis in two patients with multiple sclerosis following interferon beta treatment. Journal of Neurology, Neurosurgery & Psychiatry 2004;75:1079.

Hepatitis C and Myasthenia Gravis

34g. Readig PJ, Newman PK. Untreated hepatitis C may provoke myasthenia gravis. Journal of Neurol Neurosurg Psychiatry 1998;64(6):820.

34h. Eddy S, Wim R, Peter VE, et al. Myasthenia gravis: another autoimmune disease associated with hepatitis C virus infection. Digestive Diseases and Sciences 1999;4(1):186-189.

Bone Marrow Transplant

35. Smith CI, Aarli JA, Biberfeld, et al. Myasthenia gravis after bone marrow transplantation: evidence for a donor origin. N Engl J Med 1983;309:1565-1568.

36. Smith CI, Aarli JA, Hammarstrom L, Persson MA. IgG subclass distribution of myasthenia gravis thymoma-associated antiskeletal muscle antibodies. Neurology 1984;34:1094-1096.

37. Seely E, Drachman D, Smith BR, Antin JH, Ginsburg D, Rappaport JM. Post bone marrow transplantation (BMT) myasthenia gravis: evidence for acetylcholine receptor abnormality. Abstract. Blood 1984;64 suppl 1:221a.

38. Bolger GB, Sullivan KM, Spence AM, Appelbaum FR, Johnston R, Sanders JE, Deeg HJ, Witherspoon RP, Doney KC, Nims J, Thomas ED, Storb R. Myasthenia gravis after allogeneic bone marrow transplantation: relationship to chronic graft-versus-host disease. Neurology 1986;36:1087-1091.

39. Nelson KR, McQuillen MP. Neurologic complications of graft-versus-host-disease. Neurol Clin 1988;6:389-403.

40. Smith CI, Norberg R, Moller G, Lonnqvist B, Hammarstrom L. Autoantibody formation after bone marrow transplantation. Comparison between acetylcholine receptor antibodies and other autoantibodies and analysis of HLA and Gm markers. Eur Neurol 1989;29:128-134.

41. Hayashi M, Matsuda O, Ishida Y, Kida K. Change of immunological parameters in the clinical course of a myasthenia gravis patient with chronic graft-versus-host disease. Acta Paedriatr Jpn 1996;38:151-155.

42. Grau JM, Casademont J, Monforte R, Marin P, Granena A, Rozman C, Urbano-Marquez A. Myasthenia gravis after allogeneic bone marrow transplantation: report of a new case and pathogenetic considerations. Bone Marrow Transplant 1990;5:435-437.

43. Zaja F, Russo D, Silvestri F, Barrillari G, Fanin R, Cerno M, Marchini C, Baccarani M. Myasthenia gravis after allogeneic bone marrow transplantation: a case report. Bone Marrow Transplantation 1995;15:649-653.

44. Adams C, August CS, Maguire H, Sladky JT. Neuromuscular complications of bone marrow transplantation. Pediatr Neurol 1995;12:58-61.

Hypermagnesemia

45. Krendel DA. Hypermagnesemia and neuromuscular transmission. Robert Pascuzzi, Ed. Semin Neurol 1990;10:42-45.

46. Fuchs-Buder T, Tassonyi E. Magnesium sulphate enhances residual neuromuscular block induced by vecuronium. Br Journal of Anaesthesia 1996;76:565-566.

47. Randall RE, Cohen MD, Spray CC, Rossmeise EC. Hypermagnesemia in renal failure. Ann Int Med 1964;61:73-88.

48. Castlebaum AR, Donofrio PD, Walker FO, Troost BT. Laxative abuse causing hypermagnesemia quadriparesis and neuromuscular junction defect. Neurology 1989;39:746-747.

49. Mordes JP, Wacker WEC. Excess magnesium. Pharmacology Review 1978;29:273-300.

50. Lemcke B, Fucks C. Magnesium load induced by ingestion of magnesium-containing antacids. Contrib Nephrol 1984;38:185-194.

51. Collins EN, Russell PW. Fatal magnesium poisoning. Cleveland Clinic Quarterly 1949;16:162-166.

52. Flowers CJ. Magnesium in obstetrics. American Journal of Obstetrics and Gynecology 1965;91:763-776.

53. Pritchard JA. The use of magnesium sulfate in preeclampsia/eclampsia. Journal of Reproductive Medi cine 1979;23:107-114.

54. Lipsitz PJ. The clinical and biochemical effects of excess magnesium in the newborn. Pediatrics 1971;47:501-509.

55. Fishman RA. Neurological aspects of magnesium metabolism. Arch Neurol 1965;12:562-596.

56. Somjen G, Hilmy M, Stephen CR. Failure to anesthetize human subjects by intravenous administration of magnesium sulfate. Journal of Pharmacology and Experimental Therapeutics 1966;154:652-659.

57. Hutter OF, Kostial K. Effect of magnesium and calcium ions on the release of acetylcholine. Journal of Physiology 1954;124:234-241.

58. Del Castillo J, Engback L. The nature of the neuromuscular block produced by magnesium Journal of Physiology 1954;124:370-384.

59. Swift TR. Weakness from magnesium containing cathartics. Muscle & Nerve 1979;2:295-298.

60. De Silva AJC. Magnesium intoxication: an uncommon cause of prolonged curarization. British Journal of Anesth 1973;45:1228-1229.

61. Ghoneim MM, Long JP. The interaction between magnesium and other neuromuscular blocking agents. Anesthesiology 1970;32:23-27.

62. Bashuk RG, Krendell DA. Myasthenia gravis presenting as weakness after magnesium administration. Muscle & Nerve 1987;10:666.

63. Cohen BA, London RS, Goldstein PJ. Myasthenia gravis and preeclampsia. Obstetrics and Gynecology 1976;48:35S-37S.

64. George WK, Han CL. Calcium and magnesium administration in myasthenia gravis. Lancet 1962;2:561.

65. Gutmann L, Takamori M. Effect of magnesium on neuromuscular transmission in the Eaton-Lambert syndrome. Neurology 1973;23:977-980.

66. Streib EW. Adverse effects of magnesium salt cathartics in a patient with the myasthenic syndrome. Ann Neurol 1977;2:175-176.

67. Ross RM, Baker T. An effect of magnesium on neuromuscular function in parturients. J Clin Anesth 1996;8:202-204.

68. Alfrey AC, Terman DS, Brettschneider L, et al. Hypermagnesemia after renal homotransplantation. Ann Int Med 1970;73:367-371.

69. Layzer RB. Mineral and electrolyte disorders. Neuromuscular manifestations of systemic disease. Philadelphia: FA Davis 1985:47-78.

70. Critchley M, Herman KJ, Harrison M, Shields RA. Value of exchangable electrolyte measurement in the treatment of myasthenia gravis. Journal of Neurol Neurosurg and Psych 1977;40:250-252.

71. Jenkins RB, Witorsch P, Smythe NPD. Aspects of treatment of crisis in myasthenia gravis. Southern Medical Journal 1970;63:1127-1130.

72. Wirguin I, Brenner T, Shinar E, Argov Z. Citrate-induced impairment of neuromuscular transmission in human and experimental autoimmune myasthenia gravis. Ann Neurol 1990;27:328-330.

Botulinum Toxin

73. Linial M. Bacterial neurotoxins--a thousand years later. Isr J Med Sci 1995;10:591-595.

74. Montecucco C, Schiavo G, Tugnoli V, de Grandis D. Botulinum neurotoxins: mechanism of action and therapeutic applications. Mol Med Today 1996;10:418-424.

75. Perie S, Lacau St-Guily J. Mode of action and effects of botulinum neurotoxin A. Ann Otolaryngol Chir Cervicofac 1996;113:73-78.

76. Olney RK, Aminoff MJ, Gelb DJ, Lowentein DH. Neuromuscular effects distant from the site of botulinum neurotoxin injection. Neurology 1988;38:1780-1783.

77. Holzer SE, Ludlow CL The swallowing side effects of botulinum toxin type A injection in spasmodic dysphonia. Laryngoscope 1996;106:86-92.

78. Comella CL, Tanner CM, DeFoor-Hill L, Smith C. Dysphagia after botulinum toxin injections for spasmodic torticollis: clinical and radiographic findings. Neurology 1992;42:1307-1310.

79. Girlanda T, Vita G, Nicolosi C, et al. Botulinum toxin therapy: distant effects on neuromuscular transmission and autonomic nervous system. Journal of Neurol Neurosurg and Psych 1992;55:844-845.

80. Erbguth F, Claus D, Engelhardt A, et al. Systemic effects of local botulinum toxin injections unmasks the subclinical Lambert Eaton myasthenic syndrome. Journal of Neurol Neurosurg and Psych 1993;56:1235-1236.

80a. Borodic G. Myasthenic crisis after botulinum toxin. The Lancet 1998;352(9143):1832.

80b. Cherington M. Botulism. Muscle & Nerve 1998;10:27-31.

80c. Maselli RA, Bakshi N. Botulism. AAEM Case Report 16. Muscle and Nerve 2000;23:1137-1144.

Anesthetic Agents

81. Baraka A, Afifi A, Muallem M, et al. Neuromuscular effects of halothane suxamethion and tubocurarine in a myasthenic undergoing thymectomy. Journal of Anesthesiology 1971;43:91-95.

82. Elder BF, Beal H, Dewald W, Sobb S. Exacerbation of subclinical myasthenia by occupational exposure to an anesthetic. Anesth Analg 1971;50:383-387.

83. Gage PW, Hamill OP. Effects of several inhalation anesthetics on the kinetics of postsynaptic conduc tance in mouse diaphragm. British Journal of Pharmacology 1976;57:263-272.

84. Matthews EK, Quilliam JP. Effects of central depressant drugs upon acetylcholine release. Br Journal of Pharmacology 1964;22:415-440.

85. Hirst GDS, Wood DR. On the neuromuscular paralysis produced by procaine. Br Journal of Pharmacology 1971;41:94-104.

86. Harvey AM. The actions of procaine on neuromuscular transmission. Bulletin of Johns Hopkins Hospital 1939;65:223-238.

87. Katz RL, Gissen AJ. Effects of intravenous and intraarterial procaine and lidocaine on neuromuscular transmission in man. Acta Anesthesiol Scand Suppl 1969;36:103-113.

88. Watling SM, Dasta JF. Prolonged paralysis in intensive care unit patients after the use of neuromuscular blocking agents: a review of the literature. Crit Care Med 1994;22:884-893.

89. Benzing G, Iannaccone ST, Bove KE et al. Prolonged myasthenic syndrome after one week of muscle relaxants. Pediatr Neurol 1990;6:190-196.

90. Lagassa RS, Katz RI, Peterson M et al Prolonged neuromuscular blockade following vecuronium infusion. J Clin Anesth 1990;2:269-271.

91. Vanderheyden BA, Reynolds HN, Gerold KB, et al. Prolonged paralysis after long-term infusion. Crit Care Med 1992;20:304-307.

92. Branney SW, Haenel JB, Moore FA, et al. Prolonged paralysis with atracurium infusion: a case report. Crit Care Med 1994;22:1699-1701.

93. Segredo V, Caldwell JE, Matthay MA, et al. Persistent paralysis after long-term administration of vecuronium. N Engl J Med 1992;327:524-528.

94. Gooch JL, Suchyta, MR, Baslbierz JM, et al. Prolonged paralysis after treatment with neuromuscular junction blocking agents. Crit Care Med 1991;19:1125-1131.

95. Benzing G, Bove KE. Sedating drugs and neuromuscular blockade during mechanical ventilation. JAMA 1992;267:1775.

96. Hund EF. Neuromuscular complications in the ICU: the spectrum of critical illness-related conditions causing muscular weakness and weaning failure. Journal of the Neurological Sciences 1996;136:10-16.

97. Maher J, Rutledge F, Remtulla H, Parkes A, Bernardi L, Bolton CF. Neuromuscular disorders associated with failure to wean from the ventilator. Intensive Care Med 1995;21:737-743.

Antibiotics

98. Robinson J, Molitor H. Some toxicological and pharmacological properties of gramicidin. J Pharmacol Exp Thr 1941;73:75-82.

99. Pridgen JE. Respiratory arrest thought to be due to intraperitoneal neomycin. Surgery 1956;40:571-74.

100. Benz HG, Lunn JN, Foldes FF. "Recurarisation" by intraperitoneal antibiotics. Br Medical Journal 1961;2:241-242.

101. Bodley PO, Brett JE. Postoperative respiratory inadequacy and the part played by antibiotics. Anesthesia 1962;17:438-443.

102. McQuillen MP, Canter HE, O'Rourke JR. Myasthenic syndrome associated with antibiotics. Arch Neurol 1968;18:402-415.

103. Pittinger CB, Eryasa Y, Adamson R. Antibiotic induced paralysis. Anesth Analg 1970;49:487-501.

104. Albiero L, Bamonte F, Ongini E, Parravicini L. Comparison of intramuscular effects in acute toxicity of some aminoglycoside antibiotics. Arch Int Pharma Codyn Ther 1978;233:343-350.

105. Burkett L, Bikhaze GB, Thomas KC, et al. Mutual potentiation of the neuromuscular effects of antibiotics and relaxants. Anesth Analg 1979;58:107-115.

106. Singh YN, Harvey AL, Marshall IG. Antibiotic induced paralysis of the mouse phrenic nerve hemidiaphragm preparation and reversibility by calcium and by neostigmine. Anesthesiology 1978;48:418-424.

107. Singh YN, Marshall IG, Harvey AL. Reversal of antibiotic induced muscle paralysis of 3-4-diaminopyridine. J Pharm Pharmacol 1978;32:249-250.

108. Maeno T, Enomoto K. Reversal of streptomycin induced blockade of neuromuscular transmission by 4-aminopyridine. Proc Jpn Acad 1980;56:486-491.

109. Capute AJ, Kim YI, Sanders DB. Neuromuscular blocking effects of therapeutic concentrations of various antibiotics on normal rat skeletal muscle. A quantitative comparison J Pharmacol Exp Ther 1981;217:369-378.

110. Dretchen KL, Gergis SD, Sokoll MD, et al. Effect of various antibiotics on neuromuscular transmission. European Journal of Pharmacology 1972;18:201-203.

111. Waterman PM, Smith RB. Tobramycin-curare interaction. Anesth Analg 1977;56:587-588.

112. Singh YN, Marshall IG, Harvey AL. Some effects of the aminoglycoside antibiotic amikacin on neuromuscular and autonomic transmission. British Journal of Anesthesiology 1978;50:109-117.

113. Torda T. The nature of gentamycin induced neuromuscular block. British Journal of Anesthesiology 1980;52:325-329.

114. Paradelis AG, Triantaphyllidis C, Giala MM. Neuromuscular activity of aminoglycoside antibiotics. Meth Find Exp Clin Pharmacol 1980;2:45-51.

115. Elmqvist D, Josefsson JO. The nature of the neuromuscular block produced by neomycin. Acta Physiol Scand 1962;54:105-110.

116. Dretchen KL, Sokoll MD, Gergis SD, et al. Relative effects of streptomycin on motor nerve terminal endplate. European Journal of Pharmacology 1973;22:10-16.

117. de Rosayro M, Healy TEJ. Tobramycin and neuromuscular transmission in the rat isolated phrenic nerve diaphragm preparation. Br Journal of Anesthesiology 1978;50:251-254.

118. L'Hommediau C, Stough R, Brown L, et al. Potentiation of neuromuscular weakness in infant botulism by aminoglycosides. Journal of Pediatrics 1979;95:1065-1070.

119. Santos JI, Swenson P, Glasgow LA. Potentiation of clostridium botulinum toxin by aminoglycoside antibiotics. Clinical and laboratory observations. Pediatrics 1981;68:50-54.

120. Hokkanen E, Toibakka E. Streptomycin induced neuromuscular fatigue in myasthenia gravis. Ann Clin Res 1969;1:220-226.

120a. Wasserman BN. Chronister TE. Stark BI. Saran BR. Ocular myasthenia and nitrofurantoin.. American Journal of Ophthalmology 2000;130:531-3

121. Moore B, Safani M, Keesey J. Possible exacerbation of myasthenia gravis by ciprofloxacin. Lancet 1988;1:882.

121a. Roquer J, Cano A, Seoane JL, et al. Myasthenia gravis and ciprofloxacin (letter to the editor). Acta Neurol Scand 1996;94(6):419-420.

121b. Mumford CJ and Ginsberg L. Ciprofloxacin and myasthenia gravis. BMJ1990;301:818.

122. Vial T, Chauplannaz G, Brunel P, Leriche B, Evreux JC. Exacerbation of myasthenia gravis by perfloxacin. Rev Neurol 1995;251:286-287.

123. Rauser EH, Ariano RE, Anderson BA. Exacerbation of myasthenia gravis by norfloxacin. Ann Pharmacother 1990;24:207-208.

123a Azevedo E, Ribeiro JA, Polonia J, et al., Probable exacerbation of myasthenia gravis by ofloxacin. J Neurol 1993;240:508.

124. Samuelson RJ, Giesecke AH, Kallus, Stanley VF. Lincomycin-curare interaction. Anesth Analg 1975;54:103-105.

125. Fogdall RP, Miller RD. Prolongation of a pancuroneum induced neuromuscular blockade by clindamycin. Anesthesiology 1974;41:407-408.

126. Rubbo JT, Gergis SD, Sokoll MD. Comparative neuromuscular effects of lincomycin and clindamycin. Anesth Analg 1977;56:329-332.

127. Wright JM, Collier B. Characterization of the neuromuscular block produced by clindamycin and lincomycin. Canadian Jour Physiol Pharmacol 1976;54:937-944.

128. Booij LHD, Miller RD, Crul JF. Neostigmine and 4-aminopyridine antagonism of lincomycin pancuroneum neuromuscular blockade in man. Anesth Analg 1978;57:316-322.

129. Albrecht RF, Lanier WL. Potentiation of succinylcholine-induced phase II block by vancomycin. Anesth Anal 1993;77:1300-1302.

130. Parisi AF, Kaplan MH. Apnea during treatment with sodium colistimethate. JAMA 1965;194:298-299.

131. Gold GN, Richardson AP. An unusual case of neuromuscular blockade seen with therapeutic blood levels of colistin methanesulfonate. Am J Med 1966;41:316-321.

132. Pohlmann G. Respiratory arrest associated with intravenous administration of polymyxin B sulfate. JAMA 1966;196:81-183.

133. Lindesmith LA, Baines RD, Bigelow DB, Petty TL. Reversible respiratory paralysis associated with polymyxin therapy. Ann Int Med 1968;68:38-327.

134. Pittinger C, Adamson R. Antibiotic blockade of neuromuscular function. Annu Rev Pharmacol 972;12:109-184.

135. McQuillen MP, Engbaek L. Mechanism of colistin induced neuromuscular depression. Arch Neurol 1975;32:235-238.

136. Wright JM, Collier B. The site of the neuromuscular block produced by polymyxin B and rolitetracycline. Canadian Jour Physiol Pharmacol 1976;54:926-936.

137. Durant NN, Lambert JJ. The action of polymyxin B at the frog neuromuscular junction. British Journal of Pharmacology 1981;72:41-47.

138. Viswanath DV, Jenkens HJ. Neuromuscular block of the polymyxin group of antibiotics. J Pharm Sci 1978;67:1275-1280.

139. Decker DA, Fincham RW. Respiratory arrest in myasthenia gravis with colistimatehate therapy. Arch Neurol 1971;25:141-144.

140. Herishanu Y. The effect of streptomycin and colistin on myasthenic patients. Conf Neurol 1969;31:370-373.

141. Hokkanen E. The aggregating effect of some antibiotics on the neuromuscular blockade in myasthenia gravis. Acta Neurol Scand 1964;40:346-352.

142. Argov Z, Brenner T, Abramsky O. Ampicillin may aggravate clinical and experimental myasthenia gravis. Arch Neurol 1986;43:255-256.

143. Girlanda P, Venuto C, Mangiapane R. Effect of ampicillin on neuromuscular transmission in healthy men. A single fiber electromyographic study. European Neurology 1989;29:36-38.

144. Herishanu Y, Taustein I. The electromyographic changes induced by antibiotics. Preliminary study. Conf Neurol 1971;33:41-45.

145. Cadisch R, Streit E, Hartmann K. Exacerbation of pseudoparalytic myasthenia gravis following azithromycin (Zithromax). Schweiz Med Wochenschr 1996;126:388-310.

145a. Nieman RB, Sharma K, Edelberg H, Caffe SE. Telithromycin and Myasthenia Gravis Clinical Infectious Diseases, 2003; 37 1579

145b. Jennett AM, Bali D, Jasti P, Shah B, Browning LA. Telithromycin and Myasthenic Crisis . Clinical Infectious Diseases 2006; 43:1621–1622.

145c. Perrot X, Bernard N, Vial C, Antoine JC, Laurent H, Vial T, Confavreux C, Vukusic S. Myasthenia gravis exacerbation or unmasking associated with telithromycin treatment. Neurology. 2006;26;67:2256-8.

Quinine-Quinidine

146. Weisman SJ. Masked myasthenia gravis. JAMA 1949;141:917-918.

147. Stoffer SS, Chandler JH. Quinidine-induced exacerbation of myasthenia gravis in patients with Grave's disease. Arch Int Med 1980;140:283-284.

148. Shy ME, Lange DJ, Howard JF, et al. Quinidine exacerbating myasthenia gravis: a case report and intracellular recordings. Annals of Neurology 1985;18:120.

149. Miller RD, Way WL, Ketzumg BG. The neuromuscular effects of quinidine. Proc Soc Exp Biol Med 1968;129:215-218.

150. Grogono AW. Anesthesia for atrial fibrillation effect of quinidine on muscular relaxation. Lancet 1963;2:1039-1040.

151. Way WL, Katzung BG, Larson CP. Recurarization with quinidine. JAMA 1967;200:153-154.

152. Harvey AM, Whitehill MR. Quinine as an adjuvant to prostigmine in the diagnosis of myasthenia gravis: a preliminary report. Bulletin of Johns Hopkins Hospital 1937;61:216-217.

153. Eaton LM. Diagnostic tests for myasthenia gravis with prostigmine and quinine. Proceedings at the Staff Meetings of the Mayo Clinic 1943;18:230-246.

154. Sieb JP, Milone M, Engel AG. Effects of the quinolone derivatives quinine, quinidine and chloroquine on neuromuscular transmission. Brain Research 1996;712:179-189.

Beta Blockers

155. Herishanu Y, Rosenberg P. Beta blockers and myasthenia gravis. Annals of Internal Medicine 1975;83:834-835.

156. Hughes RO, Zacharias FJ. Myasthenic syndrome during treatment with practolol. Br Med J 1976;1:460-461.

157. Coppeto JR. Timolol associated myasthenia gravis. American Journal of Ophthalmology 1984;98:244.

158. Shaivitz SA. Timolol in myasthenia gravis. JAMA 1979;242:1611-1612.

159. Verkijk A. Worsening of myasthenia gravis with timolol maleate eyedrops. Annals of Neurology 1985;17:211-212.

160. Weber JCP. Beta adreno receptor antagonist and diplopia. Lancet 1982;2:826-827.

161. Harry JD, Linden RJ, Snow HM. The effects of three beta adreno receptor blocking drugs on isolated preparations of skeletal and cardiac muscle. Br Journal of Pharmacology 1975;52:275-281.

162. Howard JF, Johnson BR, Quint SR. The effects of beta adrenergic antagonists on neuromuscular transmission in rat skeletal muscle. Society of Neuroscience Abstracts 1987;13:147.

163. Jonkers I, Swerup C, Pirskanen R, Bjelak S, Matell G. Acute effects of intravenous injection of beta-adrenoreceptor- and calcium channel antagonists and agonists in myasthenia gravis. Muscle & Nerve 1996;19:959-965.

Calcium Channel Blockers

164. Van der Kloot W, Kita H. The effects of Verapamil on muscle action potentials in the frog and crayfish and on neuromuscular transmission in the crayfish. Comp Biochem Physiol 1975;50:121-125.

165. Ribera AD, Nastuk WL. The actions of Verapamil at the neuromuscular junction. Comp Biochem Physiol 1989;93:137-141.

166. Adams RJ, Rivner MH, Salazar, Swift TR. Effects of oral calcium antagonists on neuromuscular transmission. Neurology 1984;34:132-133.

167. Bikhazi GB, Leung I, Foldes FF. Interaction of neuromuscular blocking agents with calcium channel blockers. Anesthesiology 1982;57:268.

168. Bikhazi GB, Leung I, Foldes FF. Calcium channel blockers increase potentency of blocking agents in vivo. Anesthesiology 1983;59:269.

169. Zalman F, Perloff JK, Durant NN, Campion DS. Acute respiratory failure following intravenous Verapamil in Duchenne's muscular dystrophy. American Heart Journal 1983;105:510-511.

170. Krendell DA, Hopkins LC. Adverse effect of Verapamil in a patient with the Lambert Eaton syndrome. Muscle & Nerve 1986;9:519-522.

171. Protti DA, Reisin R, Mackinley TA, Uchitel OD. Calcium channel blockers and transmitter release at the normal human neuromuscular junction. Neurology 1996;46:1391-1396.

171a. Pina Latorre MA, Cobeta JC, Rodilla F. Influence of calcium antagonist drugs in myasthenia gravis in the elderly. Journal of Clinical Pharmacy and Therapeutics 1998;23(5):680-681.

Procainamide and other cardiovascular drugs

172. Drachman DA, Skom JH. Procainamide - a hazard in myasthenia gravis. Arch Neurol 1965;13:316-320.

173. Kornfeld P, Horowich SH, Genkins G, Papatestas AE. Myasthenia gravis unmasked by antiarrhythmic agents. Mount Sinai Journal of Medicine 1976;43:10-14.

174. Campbell EDR, Montuschi E. Muscle weakness caused by bretylium tosylate Lancet 1960;2:789.

175. Dale RC, Schroeder ET. Respiratory paralysis during treatment of hypertension with trimethaphan camsylate. Arch Int Med 1976;136:816-818.

176. Wilson SL, Miller RN, Wright C, Hasse D. Prolonged neuromuscular blockade associated with trimethaphan. Case Report. Anesth Analg 1976;55:353-356.

177. Nakamura K, Koide M, Imanaga TL. Prolonged neuromuscular blockade following trimethaphan infu sion. Anesthesia 1980;35:1202-1207.

178. Poulton TJ, James FM, Lockridge O. Prolonged apnea following trimethaphan in succinylcholine. Anesthesiology 1979;50:54-56.

Statins (lipid-lowering drugs)

178a. Cartwright MS, Jeffery DR, Nuss GR, Donofrio PD. Statin-associated exacerbation of myasthenia gravis. Neurology. 2004;63:2188.

178b. Negevesky GJ, Kolsky MP, Laureno R, Yau TH. Reversible atorvastatin-associated external ophthalmoplegia, anti-acetylcholine receptor antibodies, and ataxia. Arch Ophthalmol. 2000;118:427-428.

178c. Parmar B, Francis PJ, Ragge NK. Statins, fibrates, and ocular myasthenia. Lancet. 2002;360:717.

178d. Purvin V, Kawasaki A, Smith KH, Kesler A. Statin-associated myasthenia gravis. Report of 4 cases and review of the literature. Medicine. 2006;85:82-85.

Anticonvulsants

179. Yarri Y, Pincus JH, Argov Z. Depression of synaptic transmission by diphenylhydantoin. Ann Neurol 1977;1:334-338.

180. Norris FH, Colella J, McFarlin D. Effect of diphenylhydantoin on neuromuscular synapse. Neurology 1964;14:869-876.

181. Brumlik J, Jacobs RS. Myasthenia gravis associated with diphenylhydantoin therapy for epilepsy. Canadian Journal of Neurological Sciences 1974;1:127-129.

182. Peterson HDC. Association of trimethadione therapy in myasthenia gravis. New Engl J Med 1966;274:506-507.

183. Booker HE, Chun RWM, Sanguino M. Myasthenia gravis syndrome associated with trimethadione. JAMA 1970;21:2262-2263.

184. Yarri Y, Pincus JH, Argov Z. Phenytoin and transmitter release at the neuromuscular junction of the frog. Brain Research 1979;160:479-487.

185. Osserman KE, Genkins G. Studies in myasthenia gravis: review of a 20 year experience in over 1200 patients. Mt. Sinai Journal of Medicine 1971;38:497-572.

186. Thesleff S. The effect of anesthetic agents in skeletal muscle membrane. Acta Physiologica Scandinavia 1956;37:335-349.

187. Alderdice MT, Trommer BA. Differential effects of the anticonvulsants phenobarbital, ethosuxamide and carbamazepine on neuromuscular transmission. J Pharm Exp Therap 1980;215:92-96.

188. Talamo RC, Crawford JD. trimethadione nephrosis treated with cortisone and nitrogen mustard. N Engl J Med 1963;269:15-18.

188a. Boneva N, Brenner T, Argov Z. Gabapentin may be hazardous in myasthenia gravis. Muscle Nerve 2000;23(8):1204-1208.

188b. Zaidat OO, Kaminski HJ, Berenson F, Katirji B. Neuromuscular transmission defect caused by carbamazepine. Muscle Nerve 1999;22:1293-1296

188c. Kurian MA. King MD. Antibody positive myasthenia gravis following treatment with carbamazepine--a chance association? Neuropediatrics. 2003;34:276-7

Analgesics

189. Kim YI, Howard JF, Sanders DB. Depressant effects of morphine and mipraradine on neuromuscular transmission in rat and human myasthenic muscles. Society of Neuroscience Abstracts 1979;5:482.

190. Sanders DB, Kim YI, Howard JF, et al. Intercostal muscle biopsy studies in myasthenia gravis: clinical correlations and the direct effects of drugs in myasthenic serum. Annals New York Academy of Sciences 1981;377:544-566.

191. Slaughter D. Neostigmine and opiate analgesia. Archives of Internal Pharmacodyn 1950;83:143-148.

192. Grob D. Myasthenia gravis: current status of pathogenesis, clinical manifestations and management. J Chron Dis 1958;8:536-566.

Hormonal Medication

Corticosteroids

193. Pascuzzi RM, Coslett HB, Johns TR. Long-term corticosteroid treatment of myasthenia gravis: report of 116 patients. Ann Neurol 1984;15:291-298.

194. Seybold ME, Drachman DB. Gradual increasing doses of prednisone in myasthenia gravis: reducing the hazards of treatment. New Engl J Med 1974;290:81-84.

195. Wilson RW, Ward MD, Johns TR. Corticosteroids - a direct effect at the neuromuscular junction. Neurology 1974;24:1091-1095.

196. Hoffmann WW. Antimyasthenic action of corticosteroids. Arch of Neurol 1977;34:356-360.

197. Dengler R, Rudel R, Warelas J, Birnberger KL. Corticosteroids and neuromuscular transmission. Pflugers Archives 1979;380:145-151.

198. Kim YI, Goldner MM, Sanders DB. Short term effects of prednisolone on neuromuscular transmission in normal rats and those with experimental autoimmune myasthenia gravis. J Neurol Sci 1979;41:223-224.

199. Abramski O, Aharonov A, Teitelbaum B. Myasthenia gravis and acetylcholine receptors. Arch Neurol 1975;32:684-687.

200. Cohen IR, Stavey L, Feldman M. Glucorticoids and cellular immunity in vitro. J Exp Med 1971;132:1055-1070.

201. Stavey L, Cohen IR, Feldman M. Stimulation of rat lymphocyte proliferation by hydrocortisone during the induction of cell mediated immunity in vitro. Transplantation 1974;2:173-179.

Estrogen

202. Vacca JB, Knight WA. Estrogen therapy in myasthenia gravis. Mississippi Medicine 1957;54:337-340.

203. Frenkel M, Ehrlich EN. The influence of progesterone upon myasthenia gravis. Ann Intl Med 1964;60:971-981.

204. Bikerstaff ER. Neurological complications of oral contraceptives. London Oxford University Press 1975.

205. Brittain J, Lange LS. Myasthenia gravis and levonorgestrel implant. Lancet 1995;346:1556.

Thyroid hormone

206. Maclean B, Wilson JAC. See-saw relationship between hyperthyroidism and myasthenia gravis. Lancet 1954;1:950-953.

207. Thorner MW. Relation of myasthenia gravis to hyperthyroidism. Arch Int Med 1939;64:330-335.

Eye Drugs

208. Alexander WD. Systemic effects with eye drops. Br Medical Journal 1981;282:1359.

209. Gesztes T. Prolonged apnea after suxamethonium injection associated with eye drops containing anticholinesterase agent. A case report. Br Journal of Anesth 1966;38:408-409.

Psychiatric Drugs

210. McQuillen MP, Gross M, Johns RJ. Chlorpromazine-induced weakness in myasthenia gravis. Arch Neurol 1963;8:286-290.

211. Argov Z, Yaari Y. The action of chlorpromazine at an isolated cholinergic synapse. Brain Research 1979;164:227-236.

212. Neil JF, Himmelhoch JM, Licata SM. Emergence of myasthenia gravis during treatment with lithium carbonate. Arch Gen Psychiatry 1976;33:1090-1092.

212a. Ronziere T. Auzou P. Ozsancak C. Magnier P. Senant J. Hannequin D. Myasthenic syndrome induced by lithium. Presse Medicale 2000; 29:1043-4.

213. Borden H, Clark MT, Katz H. The use of pancuronium bromide in patients receiving lithium carbonate. Can Anesth Soc J 1974;21:79-82.

214. Hill GE, Wong KC, Hodges MR. Potentiation of succinylcholine neuromuscular blockade by lithium carbonate. Anesthesiology 1976;44:439-442.

215. Vizi ES, Illes P, Ronai A, et al. The effect of lithium on acetylcholine release and synthesis. Neuropharmacology 1972;11:521-530.

Chloroquine

216. Robberecht W, Bodnarik J, Bourgeois P, van Hees J, Carton H. Myasthenic syndrome caused by a direct effect of chloroquine on neuromuscular transmission. Arch Neurol 1989;46:464-468.

217. De Bleecker J, De Reuck J, Quatacker J, et al. Persistent chloroquine-induced myasthenia. Acta Clin Belg 1991;46:401-406.

218. Sghirlanzoni A, Mantsgazza R, Mora M, et al. Chloroquine myopathy and myasthenia-like syndrome. Muscle & Nerve 1988;11:114-119.

219. Speak G. Malaria and myasthenics. Pharmaceutical Journal 1993;251:302.

IV Contrast

220. Canal N, Franceschi M. Myasthenic crisis precipitated by iothalamic acid. Lancet 1983;1:1288.

221. Chagnac Y, Hadani M, Goldhammer Y. Myasthenic crisis after intravenous administration of iodinated contrast agent. Neurology 1985;35:1219-1220.

221a. Ferrer X. Ellie E. Deleplanque B. Lagueny A. Julien J. Myasthenic crisis after intravenous injection of iodine contrast product. Presse Medicale 1992;21:1127-8.

222. Vanden Bergh P, Kelly JJ, Carter B, Munsat TL. Intravascular contrast media and neuromuscular junction disorders. Arch Neurol 1986;19:206-207.

223. Eliashiv S, Wirguin I, Brenner T, Argov Z. Aggravation of human and experimental myasthenia gravis by contrast media. Neurology 1990;49:1623-1625.

224. Frank JH, Cooper GW, Black WC, Phillips LH. Iodinated contrast agents in myasthenia gravis. Neurology 1987;37:1400-1402.

225. Abdel-Aziz A, Bakry N. The action and interaction of diphenhydramine (Benadryl) hydrochloride at the neuromuscular junction. European Journal of Pharmacology 1973;22:169-174.

225a. Nordenbo AM. Somnier FE. Acute deterioration of myasthenia gravis after intravenous administration of gadolinium-DTPA. Lancet 1992;340:1168

Miscellaneous Drugs

226. Bazzato G, Coli U, Landini S, et al. Myasthenia-like syndrome after D,L- but not L-carnitine. Lancet 1981;1:209.

227. DeGrandis D, Mezzina C, Fiaschi A, et al. Myasthenia due to carnitine treatment. Journal of Neurological Sciences 1980;46:365-371.

228. Brown PW. Results and dangers in the treatment of amebiasis. JAMA 1935;105:1319-1325.

229. Ng KF. Blockade of adrenergic and cholinergic transmissions by emetine. Br Journal of Pharmacology and Chemotherapy 1966;28:228-237.

230. Ionescu-Drinea M, Vioculescu V, Serbanescu G, Nicolau C. Association of myasthenic and neuritic symptoms following administration of antitetanic serum. Rev Roum Neurol 1973;10:239-243.

231. Ueno S, Takahashi M, Kajiyama K, et al. Parkinson's disease and myasthenia gravis: adverse effect of trihexiphenidyl on neuromuscular transmission. Neurology 1987;37:832-883.

231a. Fujimaki K. Takasaki H. Koharazawa H. Takabayashi M. Yamaji S. Baba Y. Kanamori H. Ishigatsubo Y.Idiopathic thrombocytopenic purpura and myasthenia gravis after fludarabine treatment for chronic lymphocytic leukemia. Leukemia & Lymphoma 2005; 46:1101-2.

232. Daras M, Samkoff LM, Koppel BS. Exacerbation of myasthenia gravis associated with cocaine use. Neurology 1996;46:271-272.

232a. Solak Y. Dikbas O. Altundag K. Guler N. Ozisik Y. Myasthenic crisis following cisplatin chemotherapy in a patient with malignant thymoma 2004 Journal of Experimental & Clinical Cancer Research; 23:343-4.

232b Fraenkel PG. Rutkove SB. Matheson JK. Fowkes M. Cannon ME. Patti ME. Atkins MB. Gollob JA. Induction of myasthenia gravis, myositis, and insulin-dependent diabetes mellitus

by high-dose interleukin-2 in a patient with renal cell cancer. Journal of Immunotherapy 2002;25:373-8.

233. Tsai MC, Mansour NA, Eldefrawi AT, et al. Mechanism of action of amantadine on neuromuscular transmission. Mol Pharmacol 1978;14:787-803.

234. Bossa R, Chiericozzi M, Galatulas I, Salvatore G, Teli M, Baggio G, Castelli M. The effects of roxatidine on neuromuscular transmission. In Vivo 1995;9:113-115.

235. Restivo D, Bianconi C, Ravenni R, De Grandis D. ALS and myasthenia: an unusual association in a patient treated with riluzole. Muscle Nerve 2000;23(2):294-295.

235a. Frese A. Bethke F. Ludemann P. Stogbauer F. Development of myasthenia gravis in a patient with multiple sclerosis during treatment with glatiramer acetate. Journal of Neurology 2000; 247:713.

236. Saadat K, Kaminski HJ. Ritonavir-associated myasthenia gravis. Muscle and Nerve 1998;21:399-401.

Table 1. Drugs that impair neuromuscular transmission and may increase weakness in patients with underlying neuromuscular junction disorders

Antibiotics
Aminoglycosides
tobramycin
gentamicin
netilmicin
neomycin
streptomycin
kanamycin
Fluoroquinolones
ciprofloxacin
norfloxacin
ofloxacin
Ketolides
telithromycin (Ketek)

Other antibiotics
tetracyclines
sulfonamides
penicillins
amino acid antibiotics
macrolides
azithromycin
clarithromycin
ritonavir
nitrofurantoin

Quinolones
quinidine
quinine
chloroquine
fluoquinolone antibiotics

Table 2. Drugs implicated as potentially harmful in myasthenia gravis patients based on either anecdotal case reports or in-vitro microelectrode studies (or both)

Beta blockers
propranolol
oxprenolol
timolol
practolol
atenolol
labetalol
metoprolol
nadolol

Calcium channel blockers
verapamil

Other cardiac drugs
procainamide
bretylium
trimethaphan

Anticonvulsant medication
phenytoin
barbiturates
ethosuximide
carbamazepine
gabapentin

Ophthalmologic medications
timolol
betaxolol hydrochloride.
echothiophate (a long-acting cholinesterase inhibitor used in the treatment of open angle glaucoma)

Psychiatric drugs
lithium carbonate
phenothiazines
amitriptyline
imipramine
amphetamines
haloperidol

Other drugs prescribed by neurologists
riluzole
glatiramer acetate

Miscellaneous Drugs
fludarabine
cisplatin
interleukin-2