

Medications and Myasthenia Gravis

(A Reference for Health Care Professionals)

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Prepared for the Myasthenia Gravis Foundation of America

August, 2012

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 erythematosus, 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 erythematosus, 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

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.

Other Immunomodulators

Etanercept

Etanercept is a tumor necrosis factor-alpha (TNF-alpha) inhibitor that is used to treat autoimmune disease. A study by Rowin et al. showed that the drug may improve MG symptoms.^{44a} Of note, two case reports have suggested a correlation between etanercept and development of MG. Authors noted two patients who developed weakness 7-8 months and 6 years after beginning etanercept therapy, which resolved after 5 and 1 month of discontinuation of the drug.^{44n,44c}

Imiquimod

Another immunomodulator that may be associated with MG development is imiquimod. Imiquimod induces various cytokines that promote Th-1 cell differentiation. Th-1 cells then produce TNF-alpha, which promote B cell growth and expression of AChR-antibodies. Wolfe et al. suggest that this mechanism may explain the development of MG symptoms in a patient taking imiquimod for squamous cell carcinoma. An 80 year old female patient developed muscle weakness after topical application of imiquimod for 6-weeks. Testing found that the patient was positive for AChR antibody, and her symptoms resolved with pyridostigmine. About 1.5 years later, the patient developed muscle weakness one week after restarting imiquimod, which was once again resolved with pyridostigmine.^{44d}

Tandutinib

Tandutinib is a tyrosine kinase inhibitor that is used to treat leukemia. The drug seems to affect muscarinic nonselective receptors and muscle-type nicotinic acetylcholine receptors (Millennium Pharmaceuticals, unpublished data). Participants in a study by Lehky et al. all developed abnormal repetitive nerve stimulation studies while on tandutinib (and bevacizumab) as a treatment for glioblastoma. Clinically, the patients experienced facial, neck and proximal muscle weakness. Authors postulate that tandutinib may inhibit MuSK protein, which is a tyrosine protein kinase.^{44e} Interestingly, antibodies to MuSK are associated with bulbar MG.^{44f}

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 period⁴⁶, 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 effect. 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 MG⁶²⁻⁶⁴ 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 MgSO4 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

Calcium and Bisphosphonates

In spite of the crucial role of intracellular calcium concentration in ACh release little data exists 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.²

Likewise, bisphosphonates, which decrease serum calcium by inhibiting osteoclast-mediated bone resorption, have been reported to affect MG symptoms in patients.^{72a,72b} In a case report by Palin et al (2000), pamidronate seemed to precipitate the development of hand and lower extremity muscle weakness, as well as changes in speech, in a patient treated with the drug. The patient also exhibited AChR antibodies, a positive tensilon test, and improvement of symptoms with cholinesterase inhibitors.^{72a} In another case report, risedronate may have precipitated ocular myasthenia in a patient with osteoporosis. The patient's symptoms developed 6 weeks after beginning risedronate, and improved within 3 weeks of discontinuing the drug.^{72b}

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

Toxins

Botulinum

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 spasmotic 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, mild 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}

Cleistanthus Collinus

Cleistanthus collinus is a plant with toxins cleistanthin A and B. In animal models, the plant is associated with inhibition of postsynaptic acetylcholine receptors, which is reversed with neostigmine.^{80d,80e} The toxin is also associated with cardiac arrhythmias and metabolic acidosis.^{80f} In a case report by Damaodaram et al, a patient developed bilateral ptosis, facial and proximal muscle weakness, and respiratory failure after consuming the plant as well as alcohol. Within one hour of admission of neostigmine and atropine, ptosis resolved and the power in all limbs became normal.^{80g}

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, streptomycin¹¹⁶ 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, development of muscle weakness in subclinical MG patients and, from *in vitro* studies, to adversely affect neuromuscular transmission. Acute worsening of MG has been reported following administration of ciprofloxacin, a flurooroquinolone.^{121,121a,121b} Exacerbation of MG has been reported with use of perfloxacin, ofloxacin, and also norfloxacin.^{122,123,123a} A patient with AChR antibodies but no previous MG symptoms reportedly developed muscle weakness after use of prulifloxacin, a newer generation of fluoroquinolone.^{121c}

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. Telithromycin'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 7 of 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

Class Ia Antiarrhythmics

Class Ia drugs affect heart rhythm by inhibiting sodium channels and increasing action potential duration. The drugs have also been found to block Ach receptors, either by blocking nicotinic or muscarinic Ach receptor-mediated signaling or in the NMJ.^{145d,145e} This class includes the drugs quinidine, procainamide, cibenzoline, disopyramide and others.

It has been shown that quinidine and its stereoisomer quinine can aggravate weakness in MG.¹⁴⁶ A number of reports suggest that 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.

Procainamide can also 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

There have been anecdotal reports of cibenzoline and disopyramide potentiating MG. Specifically, there have been several reports of patients with renal disorder developing MG-like symptoms while having elevated levels of the drug (around 2,000 ng/mL), which is metabolized by the kidneys.^{177a,177b} Finally, disopyramide has been reported to exacerbate ocular-type MG, as well as potentiate MG within three days of administration to a patient with generalized MG.^{177c,177d}

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, labetolol, 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 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.

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

Hyperthyroidism and hypothyroidism can be associated with increasing myasthenic weakness.^{206,207} Similarly, the treatment of thyroid disorders may potentiate the development of MG. 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 clinical exacerbation temporally associated with 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 amoebicide 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 with renal cell carcinoma was reported to develop myasthenia gravis, myositis, and insulin-dependent diabetes mellitus in the setting of high-dose interleukin.**^{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 affect 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. Reynaud 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, Tsibiri 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, Tsikou 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 la 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. Borga 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;44(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 Paediatr 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.

Other Immunomodulators

- 44a. Rowin J, Meriggioli MN, Tuzun E, Leurgans S, Christadoss P. Etanercept treatment in corticosteroid-dependent myasthenia gravis. Neurology 2004; 63:2390-2392.
- 44b. Galassi G, Ariatti A, Codeluppi L, Meletti S. Comment on Myasthenia Gravis associated with TNF-alpha receptor blockers: a multifaceted issue. Muscle and Nerve 2010; 42(2): 296-297.

- 44c. Fee DB, Kasarskis EJ. Myasthenia gravis associated with etanercept therapy. *Muscle and Nerve* 2009; 39(6): 866-870.
- 44d. Wolfe CM, Tafuri N, Hatfield K. Case Reports: Exacerbation of myasthenia gravis during imiquimod therapy. *Journal of Drugs in Dermatology* 2007; 6(7): 745-746.
- 44e. Lehky TJ, Iwamoto FM, Kreisl TN, Floeter MK, Fine HA. Neuromuscular junction toxicity with tandutinib induces a myasthenic-like syndrome. *Neurology* 2011; 76(3): 236-241.
- 44f. Farrugia ME, Robson MD, Clover L, Anslow P, Newsom-Davis J, Kennett R, Hilton-Jones D, Matthews PM, Vincent A. MRI and clinical studies of facial and bulbar muscle involvement in MuSK antibody-associated myasthenia gravis. *Brain* 2006; 129: 1481-1492.

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 quadripareisis 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 Medicine* 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.
- 72a. Palin SL, Singh BM. Primary hypothyroidism due to a parathyroid adenoma with subsequent myasthenia gravis. QJM 2000; 93: 560-1.
- 72b. Sandanshiv RV, Neugebauer M. Risedronate induced transient ocular myasthenia. J Postgrad Med 2007; 53(4): 274-275.

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, Lowenstein 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 spastic dysphonia. Laryngoscope 1996;106:86-92.
78. Comella CL, Tanner CM, DeFoor-Hill L, Smith C. Dysphagia after botulinum toxin injections for spastic 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.

Cleistanthus Collins

- 80d. Nandakumar NV, Vijayalakshmi KM. Experimental myasthenia gravis like neuromuscular impairment with Cleistanthus collinus leaf extract administration in rat. *Phytother Res* 1996; 10: 121-6.
- 80e. Vijayalakshmi KM, Nadakumar NV, Pagala MK. Confirmatory invivo electrodiagnostic and electromyographic studies for neuromuscular junctional blocking actions of Cleistanthus collinus leaf extract administration in rat. *Phytother Res* 1996; 10:215-9.
- 80f. Benjamin SP, Fernando ME, Jayanth JJ, Preetha B. Cleistanthus collinus poisoning. *J Assoc Physicians India* 2006; 54: 742-4.
- 80g. Damodaram P, Manohar C, Kumar DP, Mohan A, Vengamma B, Rao MH. Myasthenic crisis-like syndrome due to *Cleistanthus Collinus* poisoning. *Indian J Med Sci* 2008; 62(2): 62-64.

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 conductance 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. Elmquist 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'Hommedieu 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. *BMJ* 1990;301:818.
- 121c. Rossi M, Lusini G, Biasella A, Mazzocchio R. Prulifloxacin as a trigger of myasthenia gravis. *Journal of Neurological Sciences* 2009; 280: 109-110.
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 pancuronium 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 pancuronium 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 1972;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 colistimethate 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.
- 145d. Feldman S, Karalliedde L. Drug interactions with neuromuscular blockers. *Drug Saf* 1996; 15: 261-273.
- 145e. Yamamoto N, Ozaki T, Keida Y, Ohtsuka M, Goto T. A comparison of the binding characteristics of class I antiarrhythmic agents for human muscarinic m₁-m₃ receptors. *J Cardiovasc Pharmacol* 1999; 34: 53-59.

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, Ketzung 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 potency 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 infusion. *Anesthesia* 1980;35:1202-1207.
- 177a. Wakutani Y, Matsushima E, Son A, Shimizu Y, Goto Y, Ishida H. Myasthenialike syndrome due to adverse effects of cibenzoline in a patient with chronic renal failure. *Muscle Nerve* 1998; 21(3): 416-7.
- 177b. Ozaza Y, Takamura S, Seishi I, Kitada H, Uekihara S, Hayano S. A case of acute cibenzoline intoxication in a hemodialysis patient. *Chudoku Kenkyu* 2003; 16:335-338.
- 177c. Hirose K, Yamaguchi H, Oshima Y, Choraku M, Hirono A, Takamori N, Tamura K. Severe respiratory failure and torades de pointes induced by disopyramide in a patient with myasthenia gravis. *Internal Medicine* 2008; 47:1703-1708.
- 177d. Sekioka T, Kawanishi T, Noguchi A, Matsuura T, Akiguchi I, Kameyama M. Crisis of myasthenia gravis induced by the administration of disopyramide. *Shinkeinaika* 1983; 18:95.
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 mepipharidine 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. Glucocorticoids 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, Mantegazza 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

levofloxacin

prulifloxacin

Ketolides

telithromycin (Ketek)

Other antibiotics

tetracyclines

sulfonamides

penicillins

amino acid antibiotics

macrolides

azithromycin

clarithromycin

ritonavir

nitrofurantoin

Quinolones

quinidine

quinine

chloroquine

fluoroquinolone 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

bretlyium

trimethaphan

disopyramide

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

Botulinum toxin A

Miscellaneous Drugs

fludarabine

cisplatin

interleukin-2

interferon alpha

risedronate

imiquimod

hepatitis B vaccination

etanercept

methimazole and propylthiouracil

tandutinib

methimazole

pamidronate