Drug-induced myasthenic syndromes

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Introduction

This article includes discussion of drug-induced myasthenic syndromes. The foregoing terms may include synonyms, similar disorders, variations in usage, and abbreviations.

Overview

Drug-induced myasthenic syndromes are caused by numerous medications of various classes. D-penicillamine and interferon alpha lead to an autoimmune process similar to spontaneous myasthenia gravis, whereas many other agents produce weakness by a direct compromise of neuromuscular transmission. A particular problem in clinical practice is the deterioration of neuromuscular transmission by anesthetics and neuromuscular blocking drugs. Moreover, novel drugs may show myasthenia-like syndromes or exacerbation of preexisting myasthenia gravis during clinical studies or in post-marketing surveillance. In this article, the author draws attention to the rare occurrence of drug-induced myasthenia with a new class of anticancer drugs, the immune checkpoint inhibitors. These include the drug ipilimumab targeting cytotoxic lymphocyte-associated protein 4 (CTLA-4), and the drugs nivolumab and pembrolizumab targeting programmed cell death-1 (PD-1). Management of drug-induced myasthenia in these cases requires withdrawal of the immune checkpoint inhibitor and standard immunotherapy including high-dose steroids.

Key points

- Drug-induced myasthenic syndromes are caused by numerous medications of various classes.
- D-penicillamine and interferon alpha lead to an autoimmune process similar to spontaneous myasthenia gravis.
- Many other agents produce weakness by direct compromise of neuromuscular transmission.

Historical note and terminology

Myasthenia gravis is an autoimmune disorder characterized by fluctuating weakness of voluntary muscles, with a propensity for involvement of ocular muscles. It is the prototype for a class of diseases referred to as neuromuscular transmission disorders. Within this group are Lambert Eaton syndrome, congenital myasthenic syndromes, botulism, and a wide array of drug-induced myasthenic syndromes. The pathogenic link of all these conditions is a reduction of the safety factor for neuromuscular transmission leading to weakness, which is often characterized by premature fatigue.

For almost 5 decades, certain therapeutic agents have been known to interfere directly with neuromuscular transmission (See Table 1), by affecting either presynaptic or postsynaptic function. The earliest and most commonly reported manifestation of drug-induced neuromuscular blockade was preoperative or postoperative short-lasting respiratory distress, with delayed recovery of spontaneous respiration after administration of certain aminoglycoside antibiotics (Pridgen 1956; Argov and Mastaglia 1979). Psychotropic drugs of the phenothiazine family were later found to be capable of acting in a similar way (McQuillen et al 1963). Many more drugs were subsequently discovered to have direct effects at the neuromuscular junction. Such agents may cause weakness directly, unmask subclinical myasthenia gravis, or aggravate preexisting myasthenia gravis (an up-to-date list of these potential drug-disorder interactions is maintained on the website of the Myasthenia Gravis Foundation of America ). In preexisting myasthenia gravis, as a rule of thumb, stable patients are much less likely to experience drug-induced aggravation than those with an unstable condition.

The focus of this review is medications suspected to produce an autoimmune reaction leading to myasthenia gravis.
There are 2 widely accepted offending agents (D-penicillamine and interferon alpha) (Pascuzzi 2007) although scattered reports exist for other drugs. First recognized 20 years ago (Buchnall et al 1975) and repeatedly confirmed (Vincent et al 1978; Vincent and Newsom-Davis 1982; Liu and Bienfang 1990; Drosos et al 1993; Raynauld et al 1993; Andonopoulos et al 1994; Bruggemann et al 1996), D-penicillamine causes a condition identical to autoimmune myasthenia gravis in patients with rheumatoid arthritis. There are also reports of myasthenia gravis associated with D-penicillamine treatment for scleroderma (Drosos et al 1993) and for Wilson disease (Czlonkowska 1975; Masters et al 1977). Interferon alpha-induced autoimmune myasthenia gravis was first reported in 1995 in a patient being treated for leukemia (Perez et al 1995). Since then, case reports have implicated interferon alpha in causing myasthenia gravis during the treatment of malignancy (Batochi et al 1995; Lensch et al 1996) or chronic active hepatitis C (Mase et al 1996; Piccolo et al 1996). The development of autoimmune diseases after treatment with interferon alpha is most likely caused by the drugs' immunostimulatory effects (Congeni and Kirkpatrick 2013).

Clinical manifestations

Presentation and course

Drug-induced myasthenic syndromes are characterized by progressive, and typically symmetric, muscle weakness. The most common manifestations are those of autoimmune myasthenia gravis; ptosis, diplopia, dysphagia, and dysarthria as well as weakness of the limbs and respiratory muscles with characteristic premature fatigue. The clinical pattern varies with different drugs, and not all of the symptoms are present in individual cases. Isolated ocular symptoms and unilateral ptosis have been described (Liu and Bienfang 1990; Raynauld et al 1993), and in rare instances, bilateral facial weakness may occur (Schumm et al 1981; Sghirlanzoni et al 1988).

Symptoms and signs of the myasthenic syndrome can appear days to months after institution of the offensive drug. With D-penicillamine, symptoms usually start 4 months to 9 months after initiation of treatment (Buchnall et al 1975; Andonopoulos et al 1994) but occasionally as late as 5 years to 8 years into therapy (Masters et al 1977; Liu and Bienfang 1990). The symptoms are generally mild and may be limited to extraocular muscles. Similar to D-penicillamine, the effects of interferon alpha are delayed 6 months to 9 months from initiation of the drug (Piccolo 1996). Myasthenic crisis has been reported in relation to interferon alpha therapy (Konishi 1996).

Most patients with D-penicillamine-induced myasthenia gravis have increased serum levels of anti-AChR antibodies (Masters et al 1977; Vincent et al 1978). Moreover, after D-penicillamine withdrawal serum antibodies decrease in parallel with clinical improvement, suggesting a reversible effect of the drug on the immune system rather than the unmasking of a latent myasthenia gravis. In addition, electrophysiological studies have shown reduced miniature endplate potential amplitude, and morphological studies have shown reduced bungarotoxin binding, changes typical of acquired myasthenia gravis (Vincent et al 1978). In summary, most features of D-penicillamine-induced myasthenia are similar to those of generalized idiopathic myasthenia gravis of recent onset (less than 4-months duration), although the titers of anti-AChR antibodies are significantly higher in longstanding idiopathic myasthenia gravis than in the D-penicillamine-induced disorder (Vincent and Newsom-Davis 1982). Also, HLA antigens Bw35 and DR1 are associated with D-penicillamine-induced myasthenic syndrome; the relative absence of DR4 suggests that this disorder is genetically distinct from rheumatoid arthritis (Garlepp et al 1983). Therapeutic tests with edrophonium or neostigmine produce dramatic improvement of symptoms and signs. Recovery from D-penicillamine-related myasthenia takes place within 2 to 6 months after withdrawal of the drug and may occur spontaneously without additional therapy; anticholinesterase drugs usually can be discontinued without any recurrence of the myasthenic symptoms. In contrast, other drug-induced myasthenic syndromes, anticholinesterase therapy is usually of benefit to the patient. Unless the clinical picture is severe, immunosuppressive therapy is not required for treatment.

Anecdotal evidence, often based on single case reports, suggests that other agents can produce autoimmune reactions similar to D-penicillamine and interferon alpha. Two patients with multiple sclerosis were reported to develop weakness, episodic double vision, and dysphagia along with positive anti-AChR antibodies while treated with interferon beta. Both then had a favorable response to pyridostigmine. Discontinuation of interferon beta was not reported in either patient (Dionisiotis et al 2004). One patient with rheumatoid arthritis and another with systemic lupus erythematosus developed typical clinical, physiological, and pharmacological myasthenia gravis following prolonged treatment with chloroquine (Schumm et al 1981; Sghirlanzoni et al 1988). With discontinuation of the drug, AChR autoantibodies slowly disappeared, as did the clinical and electrophysiological abnormalities. Trimethadione was also reported to produce a syndrome similar to myasthenia gravis (Peterson 1966; Booker et al 1970). In a patient with rheumatoid arthritis, ritonavir, an antiretroviral medication for the treatment of human immunodeficiency virus
infection, was associated with the development of a myasthenic condition, but without antibodies against the acetylcholine receptor. It is possible that the mechanism in this case was immune-related rather than due to impaired neuromuscular transmission (Saadat and Kaminski 1998). A patient with amyotrophic lateral sclerosis treated with riluzole for 3 months developed ptosis and diplopia and had physiological and serological findings suggesting autoimmune myasthenia gravis. The condition improved after cessation of the drug (Restivo et al 2000). One patient with a known history of myasthenia gravis was reported who developed intermittent dysarthria after starting atorvastatin that resolved on discontinuation. This patient then had recurrence of dysarthria with the administration of lovastatin, pravastatin, and simvastatin. Discontinuation of each drug resulted in resolution of symptoms. Anti-AChR antibodies were found to be positive in this patient, and he responded rapidly to pyridostigmine during every episode. Of note, his creatine kinase levels were normal (Cartwright et al 2004).

It should be appreciated that drug-induced myasthenic syndromes most commonly are due to compromised neuromuscular transmission (Howard 2003) and this is usually seen with antibiotics, especially aminoglycosides (See Table 1). Weakness is the result of direct toxicity against the neuromuscular junction, so the effects are typically seen acutely after initiation of the drug, in contrast to the slower time-course of agents that induce an autoimmune response. These drugs may produce weakness regardless of their route of administration. They may worsen weakness in a known or previously subclinical myasthenic patient, or they may cause weakness in nonmyasthenic patients. The weakness is dose dependent and corresponds to serum levels of the antibodies. It is at least partially reversible with administration of cholinesterase inhibitors, calcium infusion, and aminopyridines (Pascuzzi 2007). Other antibiotics can cause disturbances of neuromuscular transmission, including the macrolides, tetracyclines, sulfonamides, penicillins, fluoroquinolones, and the monobasic amino acids clindamycin and lincomycin. The weakness induced by clindamycin and lincomycin is not readily reversible with cholinesterase inhibitors (Pascuzzi 2007). An evaluation of postmarketing reports from the United States Food and Drug Administration adverse event reporting system and a literature review revealed a total of 37 cases of myasthenia gravis exacerbation following fluoroquinolone exposure in non-ventilated patients (Jones et al 2011). The exacerbations developed a median of 1 day following exposure and manifested as generalized muscle weakness (n=20; 54%), dyspnea (n=19; 51%), myasthenic crisis requiring ventilatory support (n=11; 30%), dysphagia (n=9; 24%), diplopia (n=6; 16%), ptosis (n=6; 16%), and death (n=2; 5%). Accordingly, physicians should carefully weigh the benefit and risks of fluoroquinolones when treating infections in non-ventilated myasthenic patients.

The antifungal agent voriconazole led to severe exacerbation of previously stable generalized myasthenia gravis in a 52-year-old woman (Azzam et al 2013). A ligand-protein docking software showed in silico that voriconazole binds to AChR and may putatively block it (Deftereos 2014). The significance of this molecular docking approach was, however, challenged. It may be necessary to employ more detailed molecular dynamics simulation in silico studies or to measure affinities in vitro.

Advances in the understanding of immune dysregulation in cancer have led to the development of a new class of anticancer drugs, the immune checkpoint inhibitors. These include the drug ipilimumab targeting cytotoxic lymphocyte-associated protein 4 (CTLA-4), and the drugs nivolumab and pembrolizumab targeting programmed cell death-1 (PD-1). Neurologic side effects of these drugs are rare but include cases of autoimmune disorders such as immune polyneuropathies, Guillain Barré syndrome, posterior reversible encephalopathy syndrome, aseptic meningitis, enteric neuropathy, transverse myelitis, immune encephalitis, as well as myasthenia gravis (Hottinger 2016). Management of these adverse effects requires withdrawal of the immune checkpoint inhibitor and high-dose steroids. If there is no clinical improvement, more potent immunosuppressive or immunomodulatory agents may be considered.

In particular ipilimumab, a novel FDA-approved recombinant human monoclonal antibody that blocks cytotoxic T-lymphocyte antigen-4 (CTLA-4) and is being used to treat patients with metastatic melanoma and other malignancies, has been reported to induce myasthenia gravis (Liao et al 2014; Johnson et al 2015; Loochtan et al 2015). These case reports are of particular interest because genetic variants in CTLA-4 have been associated with increased susceptibility to acetylcholine receptor antibody-positive myasthenia gravis, which builds a bridge between drug-induced and autoimmune forms of myasthenia (Renton et al 2015).

Severe weakness, dysphagia, and difficulties chewing and swallowing occurred in 4 of 20 patients receiving dialysis for chronic renal failure who were treated with D,L-carnitine to correct their high plasma triglyceride levels (De Grandis et al 1980). Neurophysiological investigations revealed impairment of neuromuscular transmission. The symptoms
appeared earlier and were more severe in 2 patients with underlying uremic polyneuropathy. In all patients, symptoms and signs resolved 4 to 5 days after carnitine treatment was discontinued, and did not recur when L-carnitine alone (rather than D,L-carnitine) was given (Bazzato et al 1981).

Parenteral magnesium supplementation can lead to worsening of myasthenia gravis or, if administered too liberally, can even induce weakness. The common settings for weakness to occur in nonmyasthenic patients are renal failure and pregnancy with pre eclampsia and eclampsia. As serum levels of magnesium rise above 5 mEq/L, deep tendon reflexes are typically diminished. When the level reaches 9 to 10 mEq/L, the reflexes are usually absent, and patients become severely weak (Flowers 1965). Contrary to autoimmune myasthenia gravis, extraocular muscles tend to be spared.

Botulinum toxin can affect the neuromuscular junction at sites far from injection. Dysphagia occurs frequently after injection for spasmodic dysphonia and has also been shown to occur in patients injected for cervical dystonia (Comella et al 1992). Botulinum toxin treatments may worsen myasthenia gravis.

The drugs listed in Table 1 have been described to compromise neuromuscular transmission (Pascuzzi 2007).

### Table 1. Drugs that Compromise Neuromuscular Transmission

<table>
<thead>
<tr>
<th>Type of drug</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anesthetics</td>
<td>General anesthetics: benzodiazepines, ketamine, propanediol ether, proparacaine, methoxyflurane and others</td>
</tr>
<tr>
<td></td>
<td>Local anesthetics: lidocaine, procaine, and others</td>
</tr>
<tr>
<td></td>
<td>Neuromuscular blocking drugs: vecuronium, atracurium, succinylcholine, and others</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Aminoglycosides: gentamicin, tobramycin, kanamycin, neomycin, streptomycin, netilmicin</td>
</tr>
<tr>
<td></td>
<td>Fluoroquinolones: levofloxacin, moxifloxacin, ciprofloxacin, ofloxacin, gatifloxacin, norfloxacin, trovafloxacin, pefloxacin, and prulifloxacin (Jones et al 2011)</td>
</tr>
<tr>
<td></td>
<td>Ketolides: telithromycin (Perrot et al 2006)</td>
</tr>
<tr>
<td></td>
<td>Macrolides: erythromycin, azithromycin, clarithromycin</td>
</tr>
<tr>
<td></td>
<td>Polypeptide antibiotics: vancomycin, colistin, polymyxin B</td>
</tr>
<tr>
<td></td>
<td>Penicillins</td>
</tr>
<tr>
<td></td>
<td>Tetracyclines</td>
</tr>
<tr>
<td></td>
<td>Sulfonamides</td>
</tr>
<tr>
<td></td>
<td>Others: clindamycin, nitrofurantoin, ritonavir</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Phenytoin, mephenytoin, trimethadione, ethosuximide, barbiturates, carbamazepine, gabapentin, benzodiazepines</td>
</tr>
<tr>
<td>Antifungal agents</td>
<td>Voriconazole</td>
</tr>
<tr>
<td>Anti-rheumatics</td>
<td>Chloroquine</td>
</tr>
<tr>
<td>Cardiovascular drugs</td>
<td>Beta-blockers: propranolol, oxprenolol, timolol, practolol, atenolol</td>
</tr>
<tr>
<td></td>
<td>Calcium channel blockers: verapamil</td>
</tr>
<tr>
<td></td>
<td>Others: quinidine, quinine, procainamide, bretylum, trimetaphan</td>
</tr>
<tr>
<td>Ophthalmic medications</td>
<td>Timolol, betaxolol, echothiopate</td>
</tr>
<tr>
<td>Hormonal medications</td>
<td>Corticosteroids (cave early exacerbations with high-dose therapy), estrogen</td>
</tr>
<tr>
<td>Neurologic drugs</td>
<td>Trihexyphenidyl, riluzole, botulinum toxin</td>
</tr>
<tr>
<td>Psychiatric drugs</td>
<td>Phenothiazines, lithium</td>
</tr>
<tr>
<td>Others</td>
<td>Statins (Purvin et al 2006), D-L-carnitine, tropicamide, iodinated radiographic contrast, magnesium sulfate, tandutinib, immune checkpoint inhibitors including ipilimumab, nivolumab, pembrolizumab, and ipilimumab</td>
</tr>
</tbody>
</table>

### Prognosis and complications

The prognosis is good, with complete recovery expected when the causative agent is discontinued. Recovery may occur within days to up to 18 months following discontinuation of therapy (Bruggemann et al 1996). Neither spontaneous recovery during continued therapy with the offensive drug nor permanent complications have ever been reported. If drug exposure unmaskes myasthenia gravis, the prognosis is related to the underlying disease.
Clinical vignette

A 70-year-old man with a history of myasthenia gravis (positive for acetylcholine receptor antibodies), hypertension, glaucoma, atrial fibrillation, and stroke was in stable condition receiving mycophenolate mofetil, furosemide, warfarin, alendronate, calcium and vitamin D. He underwent a gradual corticosteroid reduction and achieved a dose of 12.5mg every other day of prednisone when he contacted his neurologist stating that he no longer could ride his stationary bike for more than 5 minutes (previously, he did so for 20 minutes), had difficulty chewing, and severe ptosis of the left lid. Patient denied symptoms of intercurrent infection, had been compliant with reducing steroids by only 5 mg every month, and denied use of any new medications. Evaluation of serum electrolytes, thyroid function, and complete blood count was normal. The physician concluded that the patient was having a myasthenic exacerbation and recommended that he increase corticosteroids to 30 mg every other day. The following week, he called his neurologist to inform him that, in fact, he had started an eye drop for glaucoma the week prior to the worsening of his condition. He read on the Internet that the medication contained a beta-blocker, so he had contacted his ophthalmologist and discontinued the medication. He returned to an excellent level of functioning within the next week.

Biological basis

Etiology and pathogenesis

Myasthenia gravis is caused by autoimmune attack against proteins at the muscle endplate. About 90% of patients have antibodies directed against the acetylcholine receptor, and there is a suggestion that a muscle specific kinase may be another antigenic target. The autoimmune process arises from a breakdown in self-tolerance, producing a T cell-driven antibody production. Presumably, a combination of individual susceptibility and exposure to a toxic agent leads to breakdown in tolerance in a similar manner to spontaneous autoimmune myasthenia gravis. Agents that compromise neuromuscular transmission do so by several mechanisms: inhibiting synaptic vesicle release, acetylcholine synthesis, acetylcholine receptor activation, or cholinesterase.

The time from initiation of the offending agent to the onset of weakness provides a clue to the pathophysiology of the neuromuscular junction disorder. Weakness that begins in hours to days implies a direct toxicity of the drug at the neuromuscular junction. Conversely, a latency of several months from the initiation of a drug to onset of weakness suggests that antibodies have formed and become active at the neuromuscular junction. The temporal course and the pathophysiology of the myasthenic syndrome induced by the anti-rheumatoid drug D-penicillamine confirm that this disorder shares the same essential features as idiopathic autoimmune myasthenia gravis (Morel et al 1991). D-penicillamine has a reactive sulfhydryl group capable of modifying self-antigens and can provoke typical autoantibody-mediated myasthenia gravis, especially in DR1+ individuals. One study demonstrated that T cell clones from a DR1+ individual were highly specific for D-penicillamine but not its L-isomer or D-cysteine and were restricted to HLA-DR1. These clones also responded well to blood mononuclear cells pulsed with D-penicillamine either in the absence of serum or after chloroquine treatment but not to autologous D-pen-pulsed B cell lines. Thus, D-penicillamine may directly couple to distinctive peptides resident in surface DR1 molecules on circulating macrophages or dendritic cells (Hill et al 1999). Similarly, chloroquine can promote the production of acetylcholine receptor autoantibodies, an effect that is reversible (Schumm et al 1981; Sghiranzoni et al 1988). However, chloroquine may also produce a rapidly reversible myasthenic syndrome without autoantibodies (Bruggemann et al 1996).

Although the mechanism of interferon alpha-induced myasthenia gravis is unknown, interferon alpha therapy can induce production of autoantibodies. Studies in transgenic mice have shown that expression of interferon gamma at the motor endplate causes generalized weakness and abnormal neuromuscular junction function, which responds to cholinesterase inhibitors. Sera from those transgenic mice and from myasthenia gravis patients recognized a previously unidentified 87 kD target antigen, suggesting that expression of interferon gamma at the motor endplate provokes a humoral autoimmune response (Gu et al 1995).

Procainamide hydrochloride exerts an inhibitory effect at the postsynaptic level of the neuromuscular junction (Argov and Mastaglia 1979). Diphenylhydantoin causes a competitive neuromuscular blockade, which potentiates the action of curare; larger doses further increase the block due to either end-plate depolarization or anticholinesterase activity (Norris et al 1964). The trimethadione-induced myasthenic syndrome could be an autoimmune disorder, but anti-AChR antibodies have not been measured (Peterson 1966; Booker et al 1970). Carnitine causes a presynaptic block, and the differential response to D,L-carnitine and L-carnitine may be due to selective accumulation of D-carnitine in renal insufficiency. With high dose corticosteroids, patients with myasthenia gravis may develop an exacerbation; the
proposed mechanisms include direct effects on neuromuscular transmission, including depolarization of nerve terminals, reduced ACh release, altered miniature endplate potentials, alteration of choline transport, and intracellular potassium depletion (Pascuzzi et al 1984).

Lincomycin acts by inhibiting transmitter release presynaptically. Likewise, the aminoglycosides can act presynaptically, or they can block acetylcholine receptor binding postsynaptically. Tetracyclines act primarily at postsynaptic sites, and phenytoin and chlorpromazine exert their effects both presynaptically and postsynaptically (Argov and Mastaglia 1979).

Tandutinib is an orally active tyrosine kinase inhibitor that has been used in the treatment of leukemia and is currently under evaluation for the treatment of glioblastoma. A study in glioblastoma patients provided class III evidence that tandutinib induces reversible muscle weakness and electrophysiologic changes consistent with a myasthenic syndrome (Lehky et al 2011).

**Epidemiology**

Between 2% and 7% of patients with rheumatoid arthritis treated with D-penicillamine develop a drug-induced myasthenic syndrome (Andonopoulos et al 1994). The frequency seems to be much lower in D-penicillamine-treated patients with scleroderma (Steen et al 1986) or Wilson disease (Komal Kumar et al 2004), suggesting an underlying susceptibility to an immune-mediated process. No information is available on the incidence of other drug-induced myasthenic syndromes, but it is probably low.

**Prevention**

Avoidance of medications known to produce myasthenic syndrome is the best prevention (see table above). Because patients with DR1+ may be particularly susceptible to D-penicillamine-induced myasthenia gravis (Hill et al 1999), testing for HLA-DR1 prior to the initiation of therapy may identify potentially susceptible patients. To keep a sense of proportion, it is important to bear in mind that many of the drugs in Table 1 have only been reported in occasional patients to worsen myasthenia. Some of these anecdotal observations may be just chance coincidences. Thus, it would be inappropriate to ban the use of all these drugs, as there would be very few drugs left that patients with myasthenia could take (particularly, antibiotics).

**Differential diagnosis**

The primary diagnosis to consider in drug-induced myasthenic syndromes is the unmasking of acquired, autoimmune myasthenia gravis. Although more rare, Lambert Eaton syndrome should also be considered. Congenital myasthenic patients typically have a history of progressive weakness, often dating to birth. Stressful events, such as drug exposure, could exacerbate weakness in such patients.

**Diagnostic workup**

When the clinical presentation suggests a neuromuscular transmission disorder, the diagnostic evaluation includes edrophonium test, electromyography with repetitive nerve stimulation, and serum acetylcholine receptor antibodies. If a patient is negative for acetylcholine receptor antibodies, it may be appropriate to obtain testing for antibodies to the muscle specific kinase. Of course, a detailed history for drug exposure, which should include specific inquiry about alternative medications, should lead to the consideration of a drug-induced myasthenic syndrome.

**Management**

The best management is to discontinue the causative drug. Treatment with anticholinesterase drugs may be effective, even while the offensive drug is being administered. If treatment with the drug is resumed, the myasthenic syndrome most likely will relapse. In the case of hypermagnesemia, intravenous infusion of 1 gram of calcium gluconate over 3 minutes may provide temporary relief. If the patient has renal failure, has developed cardiac arrhythmia, or has severe hypermagnesemia, emergency dialysis is warranted.

**Special considerations**

**Pregnancy**
The primary risk for iatrogenic disease of the neuromuscular junction in pregnancy comes in the form of hypermagnesemia induced by magnesium sulfate infusion in the treatment of preeclampsia and eclampsia. Temporal weakness is typically seen after diminution of deep tendon reflexes. Therefore, it is recommended that reflexes be checked hourly during magnesium sulfate administration.

**Anesthesia**

The anesthetic management of myasthenia is challenging because many anesthetics can worsen the disease. Competitive neuromuscular blocking agents such as D-tubocurarine and depolarizing agents such as succinylcholine, should be avoided. However, mivacurium, used as a neuromuscular blocker (Paterson et al 1994), and rapid inhalation induction with halothane-nitrous oxide (Ruiz-Neto et al 1994) both have been shown to be safe and effective in myasthenic patients. Sugammadex was introduced as a novel drug in anesthetics. It is a modified l-cyclodextrin that is able to encapsulate steroidal neuromuscular blocking drugs. It has been shown to provide rapid reversal of deep rocuronium- and vecuronium-induced neuromuscular blockade in general patients (Duvaldestin et al 2010) and in single patients with myasthenia gravis (Unterbuchner et al 2010). Its onset time is about 10 times more rapid than that of neostigmine without the need for concomitant atropine administration. However, sugammadex has until now been tested only in small cohorts, and its exact place in anesthetic practice remains to be determined (Plaud 2009).

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**References especially recommended by the author or editor for general reading.**

**Former authors**

Werner Trojaborg MD PhD (original author), Linda Chang MD, Daniel Koontz MD, and Henry Kaminski MD

**ICD and OMIM codes**

**ICD codes**

ICD-9:

- Myasthenia gravis without (acute) exacerbation: 358.00
- Myasthenia gravis with (acute) exacerbation: 358.01

ICD-10:

- Myasthenia gravis: G70.0

**Profile**

**Age range of presentation**

- 0-01 month
- 01-23 months
- 02-05 years
- 06-12 years
- 13-18 years
- 19-44 years
- 45-64 years
- 65+ years

**Sex preponderance**

female>male, >1:1

**Family history**

none

**Heredity**

none

**Population groups selectively affected**

none selectively affected
Occupation groups selectively affected

none selectively affected

Differential diagnosis list

acquired myasthenia gravis
congenital myasthenia
Lambert Eaton syndrome

Associated disorders

Chronic renal failure
Eclampsia
Hepatitis C
HIV infection
Hypercholesterolemia
Hypermagnesemia
Leukemia
Preeclampsia
Rheumatoid arthritis

Other topics to consider

Lambert-Eaton myasthenic syndrome
Myasthenia gravis
Wilson disease

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