The Challenge of Pain Management in Patients With Myasthenia Gravis

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Elyad Davidson

ABSTRACT. Myasthenia gravis (MG) is an autoimmune disorder of the neuromuscular junction. The complexity of the disease and its treatments make MG patients particularly susceptible to adverse effects of drugs. MG is not a painful condition; however, as pain management armamentarium includes drugs from diverse pharmacological groups and with potential for drug-drug interactions, managing pain in patients with MG can be challenging. The underlying disease and the concomitant medications of each patient must be considered and the analgesic treatment individualized. This review presents an update on the various aspects of pain pharmacotherapy in patients with MG, focusing primarily on medications used to treat chronic pain. Drugs discussed are opioids, nonsteroidal anti-inflammatory drugs, antidepressants, anticonvulsants, muscle relaxants, benzodiazepines, intravenous magnesium, and local anesthetics. Drug interactions with agents used for MG treatment (acetylcholinesterase inhibitors, corticosteroids, immunosuppressants) and plasmapheresis are discussed. The clinical usefulness and limitations of each of the drug classes and agents are described.

KEYWORDS. acetylcholinesterase inhibitors, adverse effects, anticonvulsants, antidepressants, benzodiazepines, corticosteroids, drug-drug interactions, immunosuppressants, local anesthetics,
magnesium, muscle relaxants, myasthenia gravis, nonsteroidal anti-inflammatory drugs, NSAIDs, opioids, pain, pharmacotherapy, plasmapheresis

**MYASTHENIA GRAVIS**

In 1692 the physiologist Thomas Willis first described patients with weakness of limb muscles increasing over time, a disorder known today as myasthenia gravis (MG). The clinical presentation of MG includes a history of progressive muscle weakness and fatigue during repeated or sustained activity. The most common muscles to be affected are extraocular, limb, facial expression, and neck muscles. MG has a prevalence of 85 to 125 per million and it can present at any age; however, there is a bimodal peak of incidence, with the first peak in the third decade (predominantly affecting women) and the second peak in the sixth and seventh decades (predominantly affecting men).1,2

**Pathophysiology**

MG is an established antibody-mediated, autoimmune disorder of the neuromuscular junction (NMJ).1 The NMJ is a synapse, which consists of presynaptic nerve terminal that releases neuronal vesicles containing acetylcholine (ACh) that activate nicotinic subtype of acetylcholine receptors (AChRs), which are located at the postsynaptic skeletal muscle cell membrane. The AChR, upon activation, opens ion channel (mainly for sodium) that induce generation of depolarization, resulting in muscle contraction.3 The synaptic space consists of a variety of regulatory proteins including acetylcholine esterase (AChE) enzymes, the main regulators of ACh levels in the neuromuscular synapse. The histological hallmarks of MG include a decrease of about 65% in the number of AChRs, and widening of the synaptic space while normal presynaptic nerve terminal is preserved.4 The nicotinic AChR of skeletal muscle is the target of the autoimmune response in MG. The majority of MG patients are seropositive for AChR autoantibodies, whereas 10% to 20% are AChR antibody seronegative.5 These seronegative patients with myasthenic symptoms may have antibodies to other targets at the NMJ, including (1) muscle specific kinase (MuSK) in MG, (2) presynaptic voltage-gated calcium channels in the Lambert–Eaton myasthenic syndrome, and (3) voltage-gated potassium channels in acquired neuromyotonia (reviewed extensively by Vincent and Leite6). The pain management considerations are similar in above-mentioned different myasthenic syndromes, therefore, this review will not differentiate between them in regard to pain pharmacotherapy.

**Treatment**

Modern treatment of MG gravis is highly effective, leading to reduction of mortality from the disease practically to zero.1 In general, the current treatments include (1) AChE inhibitors, (2) immunosuppression, (3) surgical thymectomy, (4) plasmapheresis, and (5) intravenous immunoglobulins. The initial treatment usually involves the use of the AChE inhibitors; however, additional therapy will be needed in most cases to control the disease. Often an immune system directed treatment is added, beginning with either thymectomy or high-dose corticosteroids. In the long term, steroid-sparing medications are usually added. Intravenous immunoglobulins or plasmapheresis may be effective in the early stages of the disease, before thymectomy, or later during an exacerbation.1

**Acetylcholinesterase Inhibitors**

AChE inhibitors increase the synaptic availability and prolong the duration of action of ACh on the postsynaptic receptors. AChE inhibitors are usually the first line agents in the treatment of MG and AChE monotherapy may be sufficient to treat mild disease. Pyridostigmine is the most commonly used drugs within this category.1

**Immunosuppression**

Immunosuppressive therapy is indicated when weakness is not adequately controlled by AChE inhibitors but is sufficiently distressing to outweigh the risks of possible adverse effects of immunosuppression. Corticosteroids, azathioprine, and cyclosporine...
are widely used for long-term immunosuppression in MG. Recently, mycophenolate mofetil, tacrolimus, rituximab, and etanercept have been used in the treatment of MG as “steroid sparing” agents.

**Thymectomy**

Thymectomy is performed to induce remission, or at least improvement in MG symptoms, thus permitting reduction in immunosuppressive medications. After thymectomy, nearly 80% to 85% of patients eventually experience improvement in their MG.

**Plasmapheresis**

Plasmapheresis removes antibodies from the circulation and produces short-term clinical improvement in patients with MG. It is used primarily to stabilize the condition of patients in myasthenic exacerbations or for the short-term treatment of patients undergoing thymectomy. Typically, five exchange treatments of 3 to 4 L each are carried out over a 2-week period. The effect of plasmapheresis is rapid and transient, with improvement occurring within days of treatment and lasting for few weeks.

**Intravenous Immunoglobulins**

The indications for the use of intravenous immunoglobulins are the same as those for plasmapheresis. However, it has the advantages of not requiring special equipment or large-bore vascular access. In patients who respond to immunoglobulins, the improvement begins within four to five days and the effect may sustain for weeks.

**PAIN MANAGEMENT IN MYASTHENIA GRAVIS PATIENTS**

MG is normally not a painful condition. There are no clear data indicating that incidence of chronic pain in MG is different from that of general population, with the exemption of the patients who have undergone thymectomy and suffer from chronic poststernotomy pain. However, certain pain syndromes may be more prevalent in MG patients. Age and immunosuppression are risk factors for developing herpes zoster infection and subsequent postherpetic neuralgia (PHN). Most MG patients are treated with corticosteroids or other immunosuppressive drugs, and studies have shown that patients on chronic corticosteroid and/or azathioprine treatment are at higher risk for herpes zoster infection. Although the incidence of herpes zoster was not studied separately in MG population, it is suspected to be higher in this group compared to general population, because of the long-term immunosuppressive treatment. The underlying diseases of the patient should always be considered when choosing the strategy of pain management and a judicious choice of every drug is particularly important in patients with MG. The pharmacotherapy decisions should take into account the severity of MG and its current treatment in order to minimize adverse effects and to prevent undesired drug-drug interactions. The drug-specific considerations that have to be taken into account in pain management of MG patients are summarized in Table 1 and key medications that may adversely affect MG symptoms or interact with MG treatment are summarized below.

The effects of plasmapheresis, a common treatment in MG, on the pharmacokinetics of different analgesic agents is also an important issue, because the doses of several analgesic drugs may need adjustment when the patients undergo plasmapheresis.

Plasmapheresis is usually effective in removing a substance from plasma only when specific pharmacokinetic criteria are met: (1) high (>80%) plasma protein binding and (2) low (<0.2 L/kg bodyweight) volume of distribution (Vd). Effects of plasmapheresis on the medications in pain management armamentarium are summarized in Table 2.

**Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), Paracetamol, and Dipyrone**

NSAIDs (both cyclooxygenase-2 [COX-2] selective and nonselective) are used extensively to treat both acute and chronic pain as monotherapy or in combination with other drugs.

**Effect on MG**

A search performed in PubMed, EMBASE, and MEDLINE databases on September 15th,
TABLE 1. Interactions Between Selected Analgesic Agents, MG, and its Treatment

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Drug</th>
<th>Interaction with MG or MG treatment</th>
<th>Effect</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioids</td>
<td>All opioids</td>
<td>MG</td>
<td>Opioids may depress respiration; effects potentiated by AChEIs</td>
<td>72, 73</td>
</tr>
<tr>
<td></td>
<td>Morphine, methadone, fentanyl, tramadol, buprenorphine</td>
<td>Cyclosporine</td>
<td>CYP3A4 inhibitors (cyclosporine) may decrease the metabolism of CYP3A4 substrates (methadone, buprenorphine, tramadol, methadone, fentanyl) and result in increased pharmacodynamic effects. P-gp inhibitors (cyclosporine) may inhibit the P-gp activity in the blood-brain barrier and increase the CNS concentration of P-gp substrates (morphine, methadone)</td>
<td>74, 75, 76</td>
</tr>
<tr>
<td></td>
<td>Morphine, methadone, fentanyl, tramadol, buprenorphine</td>
<td>Dexamethasone</td>
<td>CYP3A4 inducers (dexamethasone) may increase the metabolism of CYP3A4 substrates (methadone, buprenorphine, tramadol, methadone, fentanyl)</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>Tacrolimus</td>
<td></td>
<td>Both tacrolimus and methadone are reported to cause QT prolongation; concomitant use increases the risk for cardiac arrhythmias.</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>Meperidine, oxycodone, propoxyphene</td>
<td></td>
<td>No drug-drug interactions between meperidine, oxycodone, propoxyphene and MG treatments were found.</td>
<td></td>
</tr>
<tr>
<td>NSAIDs, paracetamol and dypirone</td>
<td>Aspirin and nonselective NSAIDs</td>
<td>Corticosteroids</td>
<td>Concurrent use of aspirin and dexamethasone may result in an increased risk of gastrointestinal ulceration and subtherapeutic aspirin serum concentrations. Concurrent use of NSAIDs and corticosteroids increase the risk of adverse gastrointestinal adverse effects.</td>
<td>77, 78, 79, 80, 81</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Drug class</th>
<th>Drug</th>
<th>Interaction with MG or MG treatment</th>
<th>Effect</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin and nonselective NSAIDs</td>
<td>Tacrolimus, azathioprine, mycophenolate</td>
<td>Concurrent use of NSAIDs and tacrolimus may result in acute renal failure. NSAIDs may mask fever, swelling and other signs and symptoms of an infection associated with tacrolimus, mycophenolate or azathioprine treatment. Mycophenolate may cause severe gastrointestinal side effects, use cautiously with NSAIDs.</td>
<td></td>
<td>82, 83, 84, 85</td>
</tr>
<tr>
<td>Rituximab</td>
<td></td>
<td>Rituximab may cause significant thrombocytopenia, theoretically increased risk of bleeding exists when used concomitantly with NSAIDs.</td>
<td></td>
<td>86</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Tacrolimus, azathioprine, mycophenolate</td>
<td>Concurrent use of cyclosporine and NSAIDs may result in an increased risk of cyclosporine toxicity (renal dysfunction, cholestasis, paresthesias).</td>
<td></td>
<td>24, 25, 26, 77, 78, 79, 81, 87, 88, 89, 90, 91, 92, 93</td>
</tr>
<tr>
<td>COX-2 selective NSAIDs: celecoxib, etoricoxib, rofecoxib</td>
<td>Tacrolimus, azathioprine, mycophenolate</td>
<td>Concurrent use of NSAIDs and tacrolimus may result in acute renal failure. NSAIDs may mask fever, swelling and other signs and symptoms of an infection associated with tacrolimus, mycophenolate or azathioprine treatment.</td>
<td></td>
<td>83, 84</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td></td>
<td>Concurrent use of cyclosporine and NSAIDs may result in an increased risk of cyclosporine toxicity (renal dysfunction, cholestasis).</td>
<td></td>
<td>24, 83, 94</td>
</tr>
<tr>
<td>Paracetamol and dipyrone</td>
<td>MG</td>
<td>Paracetamol and dipyrone were not found to affect MG or have significant drug-drug interaction with MG treatments.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paracetamol and dipyrone</td>
<td>Cyclosporine, tacrolimus</td>
<td>Dipyrrone has been associated with renal adverse effect; high doses should be avoided with cyclosporine and tacrolimus.</td>
<td></td>
<td>27</td>
</tr>
<tr>
<td>TCAs</td>
<td>Amitriptyline, nortriptyline, desipramine, imipramine</td>
<td>Amitriptyline interferes with neuromuscular transmission under experimental conditions and may precipitate or exacerbate MG. No significant drug-drug interactions between amitriptyline, nortriptyline, desipramine, imipramine and MG treatments were found.</td>
<td></td>
<td>95</td>
</tr>
</tbody>
</table>
### SNRI

<table>
<thead>
<tr>
<th>Medication</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duloxetine</td>
<td>Duloxetine was not found to affect MG. However, dose-dependent asthenia was reported with the clinical use of duloxetine. Due to dose-dependency of asthenia reported, duloxetine should be initiated at 30 mg/day and increased cautiously to 60 mg/day. No significant drug-drug interactions between duloxetine and MG treatments were found.</td>
</tr>
</tbody>
</table>

### Triptans

<table>
<thead>
<tr>
<th>Medication</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sumatriptan, rizatriptan</td>
<td>Triptans were not found to affect MG or have significant drug-drug interaction with MG treatments. Sumatriptan has been effectively used in alleviating headache in MG patients. It appears that triptan agents can be safely used for the treatment of migraine in MG patients.</td>
</tr>
</tbody>
</table>

### Anti-convulsants

<table>
<thead>
<tr>
<th>Medication</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine (CBZ)</td>
<td>Concurrent use of cyclosporine or tacrolimus with CBZ may result in reduced cyclosporine/tacrolimus serum levels as a result of CYP3A4 induction by CBZ</td>
</tr>
<tr>
<td>Cyclosporine, tacrolimus</td>
<td>Concurrent use of cyclosporine or tacrolimus with CBZ may result in reduced cyclosporine/tacrolimus serum levels as a result of CYP3A4 induction by CBZ</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>CBZ may potentially accelerate the hepatic metabolism of systemic corticosteroids</td>
</tr>
<tr>
<td>Gabapentin, pregabalin, CBZ</td>
<td>Gabapentin and CBZ may unmask or aggravate weakness in MG. Pregabalin share the same mechanism with gabapentin, therefore should be used with caution.</td>
</tr>
<tr>
<td>Pregabalin, gabapentin</td>
<td>Gabapentin and pregabalin were not found to interact with MG treatments.</td>
</tr>
<tr>
<td>Valproic acid, topiramate</td>
<td>Valproic acid and topiramate were not found to affect MG or have significant drug-drug interaction with MG treatments. There is high incidence of weakness reported with valproic acid therapy. As the clinical impact of weakness in MG patient may be more critical, attention should be paid on weakness development when initiating valproic acid in MG patients.</td>
</tr>
</tbody>
</table>

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*Prescribing information*

- Cymbalta oral delayed-release capsules, 2007
- Depakene oral capsules, syrup, 2006

*(Continued on next page)*
### TABLE 1. Interactions Between Selected Analgesic Agents, MG, and its Treatment (Continued)

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Drug</th>
<th>Interaction with MG or Drug treatment</th>
<th>Effect</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines</td>
<td>Clonazepam, diazepam, alprazolam</td>
<td>Cyclosporine</td>
<td>Concurrent use of several CYP3A4 substrate benzodiazepines (clonazepam, diazepam, alprazolam) and CYP3A4 inhibitors (cyclosporine) may decrease the metabolism of those benzodiazepines and result in increased bioavailability and pharmacodynamic effects. In cyclosporine-treated MG patients in whom risk to benefit ratio warrants use of benzodiazepines, those not undergoing phase-I metabolism (oxazepam, lorazepam, brotizolam) may be preferable.</td>
<td>99</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dexamethasone</td>
<td>CYP3A4 inducers (dexamethasone) may increase the metabolism of CYP3A4 substrates</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MG</td>
<td>Benzodiazepines may cause muscle weakness and depress respiration.</td>
<td>99</td>
</tr>
<tr>
<td>Local anesthetics</td>
<td>Lidocaine</td>
<td>Tacrolimus</td>
<td>Tacrolimus has been associated with a possible risk for QT prolongation and/or torsades de pointes. It should be used cautiously with drugs that may prolong the QT interval such as lidocaine.</td>
<td>58, 100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>All local anesthetics</td>
<td>CYP3A4 inducers (dexamethasone) may increase the metabolism of CYP3A4 substrates (lidocaine).</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MG, pyridostigmine, neostigmine</td>
<td>Local anesthetics can antagonize the effects of AChEIs by inhibiting neuronal transmission in skeletal muscle and inhibit the action of ACh at the motor end plate.</td>
<td>101</td>
</tr>
</tbody>
</table>
TABLE 2. Effect of Plasmapheresis on Analgesic Agents

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Drug (PPB, Vd)</th>
<th>Effect of Plasmapheresis</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioids</td>
<td>Morphi ne (low PPB: 20–36%)</td>
<td>Effective removal of these opioids by plasmapheresis is unlikely.</td>
<td>Prescribing information morphine sulfate IV injection, 2004</td>
</tr>
<tr>
<td></td>
<td>Oxycodone (low PPB: 45%)</td>
<td></td>
<td>Prescribing information OxyContin, 2007</td>
</tr>
<tr>
<td></td>
<td>Methadone (relatively high PPB: 71–88%, but also high Vd: 3.6 L/kg)</td>
<td></td>
<td>102, 103</td>
</tr>
<tr>
<td></td>
<td>Fentanyl (relatively high PPB: 80–86%, but also high Vd: 3.2–6 L/kg)</td>
<td></td>
<td>Prescribing information Duragesic, 2001; 104</td>
</tr>
<tr>
<td></td>
<td>Hydromorphone (low PPB: 20%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Propoxyphene</td>
<td>Plasmapheresis effectively removes propoxyphene from plasma; therefore additional dose may be needed after each plasmapheresis session.</td>
<td>105</td>
</tr>
<tr>
<td></td>
<td>Buprenorphine (high PPB: 96%, not very high Vd: 97–187 L)</td>
<td>Despite the lack of data on clearance by plasmapheresis, buprenorphine may be removed by plasmapheresis to higher extent than other opioids, therefore; patients should be monitored for reduced analgesic effect.</td>
<td>106</td>
</tr>
<tr>
<td></td>
<td>Diclofenac (high PPB: &gt;99%, low Vd: 0.5 L/kg)</td>
<td>Each plasmapheresis session removes 17% of diclofenac dose given before plasmapheresis.</td>
<td>Prescribing information Voltaren, 2000; 107</td>
</tr>
<tr>
<td></td>
<td>Ibuprofen (high PPB: &gt;99%, low Vd: 0.11–0.18 L/kg)</td>
<td>Ibuprofen intoxication successfully managed with plasmapheresis has been reported.</td>
<td>108, 109</td>
</tr>
<tr>
<td></td>
<td>Naproxen and ketorolac (high PPB: 99% and low Vd: &lt;0.2 L/kg)</td>
<td>Reasonable to assume that both will be removed to some extent by plasmapheresis.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Celecoxib (high PPB: 97%, but high Vd: 400L), etoricoxib (relatively high PPB: 92% and moderate Vd: 119 L)</td>
<td>No dedicated studies have evaluated the removal of selective COX-2 selective agents by plasmapheresis. Based on PPB and Vd, it can be estimated that both agents are not likely to be significantly removed by plasmapheresis.</td>
<td>Prescribing Information Celebrex, 2001; 110</td>
</tr>
<tr>
<td></td>
<td>NSAI Ds summary</td>
<td>The high protein binding and low Vd of most COX nonselective NSAIDs (but not COX-2 selective inhibitors) suggests that additional dose may be needed after each plasmapheresis session.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Paracetamol</td>
<td>Paracetamol is removed to a lesser extent (only 4.3% of the dose) by plasmapheresis; therefore there is no need for additional doses following plasmapheresis.</td>
<td>107</td>
</tr>
</tbody>
</table>

(Continued on next page)
### TABLE 2. Effect of Plasmapheresis on Analgesic Agents (Continued)

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Drug (PPB, Vd)</th>
<th>Effect of Plasmapheresis</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCAs</td>
<td>Amitriptyline Plasma concentration of amitriptyline decreases by 63% after single plasmapheresis session.</td>
<td>111</td>
<td></td>
</tr>
<tr>
<td>TCAs summary</td>
<td>Plasmapheresis is effective in the treatment of intoxications with TCAs. Therefore, we suggest additional dose of TCAs should be administered after each plasmapheresis session.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SNRI</td>
<td>Duloxetine (relatively high PPD: &gt;90%, but very high Vd: 1640 L) Based on PPD and Vd, duloxetine is unlikely to be significantly removed by plasmapheresis.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triptans</td>
<td>Triptans summary It is unknown whether triptan agents are removed by plasmapheresis. This information is possibly less relevant with triptans, since they are taken in migraine attacks per need and not chronically to achieve steady state plasma concentrations.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Gabapentin (minimal PPB, relatively low Vd: 0.8 L/kg) Gabapentin and pregabalin are minimally bound to plasma proteins; therefore these two molecules are very unlikely to be effectively removed by plasmapheresis.</td>
<td>Prescribing information Neurontin, 2007; 112, 113, 114</td>
<td></td>
</tr>
<tr>
<td>Pregabalin (minimal PPB, relatively low Vd: 0.5 L/kg) Several reports indicate that plasmapheresis is effective in removing carbamazepine. However, in an carbamazepine-treated MG patient, in whom the drug levels were measured before and after five cycles of plasmapheresis, though a reduction in the serum concentration of carbamazepine was noted, the authors conclude that alterations was not clinically significant to merit dose adjustment.</td>
<td>Prescribing information Lyrica, 2007; 113, 114, 115, 116, 117, Prescribing information Tegretol, 2002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine (moderate PPB: 76%, moderately high Vd: 0.8–2 L/kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valproic acid (relatively high PPB: 90%, low Vd: 0.14–0.23 L/kg) Theoretically, some portion of the drug should be removed by plasmapheresis; however, a report of MG patient treated with valproic acid and undergoing plasmapheresis showed that magnitude of drug loss by plasmapheresis was small, did not reach clinical importance. Therefore, it appears that there is no need for dose adjustment.</td>
<td>Prescribing information Depakote Tablets, 2002; 118, 119</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Topiramate (very low PPB: 9–41%, moderate Vd: 0.6–0.8 L/kg)

We could not find whether plasmapheresis is effective in removing topiramate from plasma. Due to low plasma protein binding it is reasonable to assume that it would not be removed significantly by plasmapheresis.

Prescribing information Topamax Tablets; 120, 121

Local Anesthetics

Lidocaine

The issue of plasmapheresis is irrelevant in the case of intravenous lidocaine administration, as there is no reason for the patient to undergo both treatments simultaneously. Plasmapheresis should not adversely affect topical lidocaine treatment, since the effect of the anesthetic is local.

Mexiletine (low PPB: 50–70%, very high Vd: 5–9 L/kg)

Mexiletine is not dialyzable in plasmapheresis, therefore no dosing adjustment is needed.

Prescribing information Mexitil, 2003; 122

Benzodiazepines

Diazepam (high PPB: >90%, but relatively high Vd: 1.3 L/kg)

Most benzodiazepines are highly bound to plasma proteins, but on the other hand, they all have volume of distribution of at least 1 L/kg. In addition, plasmapheresis is not considered an effective treatment of benzodiazepine overdose. Therefore, it can be concluded that plasmapheresis should not reduce substantially the plasma concentrations of benzodiazepines and dose adjustments are not warranted.

Prescribing information Assival injection, 123

Lorazepam (relatively high PPB: >85%, but relatively high Vd: 1.3 L/kg)

Prescribing information Ativan injection, 2002,
Prescribing information Klonopin, 1997, 124, 125

Clonazepam (relatively high PPB: 85%, but high Vd: 1.5–4.4 L/kg)

Prescribing information Versed, 1997, and 126, 127

Midazolam: (high PPB: 95%, but relatively high Vd: 1–2.5 L/kg)

Muscle Relaxants

Baclofen (minimal PPB: 35%, moderately low Vd: 59.1 L)

Based on PPB and Vd, baclofen should not be removed effectively by plasmapheresis.

128, 129

Note: PPB = plasma protein bound; Vd = volume of distribution.
2008, revealed no documentation indicating that any NSAID, paracetamol (acetaminophen), or dipyrone (metamizole) aggravate MG or cause neuromuscular weakness.

**Interactions**

Despite lack of negative effect on MG, both COX-2–selective and –nonselective NSAIDs may interact with MG medications. Concomitant administration with corticosteroids increases the risk of gastrointestinal bleeding,

\[ \text{22} \] particularly in elderly,

\[ \text{23} \] whereas combination with cyclosporine or tacrolimus may increase the risk for nephrotoxicity.

\[ \text{24} – \text{26} \] Paracetamol and dipyrone are not known to increase those risks associated with corticosteroid treatment. There are no controlled studies indicating that dipyrone increases the risk of nephrotoxicity; however, few case reports

\[ \text{27, 28} \] has raised a possibility of adversely affecting renal function. Therefore, caution should be undertaken when prescribing dipyrone in patients treated with cyclosporine, a potentially nephrotoxic drug. Paracetamol at low to medium doses was not reported to affect renal function and appears to be safe in combination with cyclosporine. On the other hand, long-term use of high doses of paracetamol (3 to 4 g/day) has been found to be associated with decrease in renal function,

\[ \text{29} \] therefore the combination of cyclosporine with chronic use of high-dose paracetamol should be avoided.

**Opioids**

Opioids are among the most effective analgesics available today and are used extensively for the treatment of acute and chronic pain conditions.

**Effects on MG**

Opioid analgesics in therapeutic concentrations do not appear to depress neuromuscular transmission in myasthenic muscle. However, central respiratory depression may be a problem with opioids.

\[ \text{30} \] Systemic opioids may be given to treat moderate to severe pain in myasthenic patient; however, the therapy should be initiated at low doses and the dose increments should be made with caution to avoid respiratory depression, which may aggravate patient’s condition.

**Interactions**

Cyclosporine was shown to be a moderate inhibitor of Cytochrome P450 (CYP450) 3A4 isoenzyme.

\[ \text{31} \] Fentanyl, methadone, tramadol, and buprenorphine, which are CYP450 3A4 substrates,

\[ \text{31} \] may theoretically interact with cyclosporine. A case report of increase in plasma concentration of fentanyl possibly caused by administration of cyclosporine was published.

\[ \text{32} \] This theoretical interaction should be kept in mind and slower dose titration with these opioids may be considered. Cyclosporine is also an inhibitor of P-glycoprotein (P-gp), which is one the best studied efflux transporters of xenobiotics in mammals.

\[ \text{33} \] It is expressed in several different organs, including the luminal membrane of the blood-brain barrier capillaries,

\[ \text{34} \] where it effluxes drugs from the central nervous system (CNS) back into the systemic circulation. Methadone, buprenorphine, and morphine are known substrates of P-gp at the blood-brain barrier.

\[ \text{35} – \text{37} \] Though there are no studies addressing the P-gp–based interaction between cyclosporine and these opioids, theoretically, cyclosporine may increase the CNS concentration of buprenorphine,

\[ \text{37} \] morphine, and methadone, similarly to another P-gp inhibitor, verapamil.

\[ \text{34} \] Therefore, CNS adverse effects of these opioids should be monitored more carefully in patients treated with cyclosporine. Oxycodone was shown not to be a P-gp substrate in rats,

\[ \text{38} \] hence should not interact with P-gp inhibitors as cyclosporine; however, there is a lack of data to eliminate this interaction is humans. Based on the mentioned above, we may suggest that oxycodone is, at least theoretically, preferred opioid for moderate to severe pain in MG patients treated with cyclosporine.

**Tricyclic Antidepressants**

Tricyclic antidepressants (TCAs) are indicated for the treatment of different neuropathic pain syndromes as painful diabetic neuropathy and PHN. Amitriptyline has been studied extensively, though other TCAs such as desipramine and nortriptyline, which have a more favorable adverse effect profile, have also shown efficacy in neuropathic pain.
Effects on MG

TCAs are known to have anticholinergic adverse effects, therefore may theoretically interfere with ACh transmission and negatively affect MG symptoms. However, these effects are mediated by blocking muscarinic, and not nicotinic ACh receptors, and include xerostomia, increase in intraocular pressure, urinary retention, and constipation. The effect of TCAs in patients with MG is largely unknown. There is a report indicating that amitriptyline interferes with neuromuscular transmission under experimental conditions, therefore potential risk exists when exposing MG patient to amitriptyline. We did not find any other evidence showing exacerbation of MG by TCAs. We have administered amitriptyline to a patient with ocular MG suffering from PHN (unpublished data). When amitriptyline dose was increased to 50 mg/day, diplopia was observed in our patient, otherwise asymptomatic with pyridostigmine, azathioprine, and prednisone treatment. Diplopia was reversible immediately upon discontinuation of amitriptyline. Amitriptyline was switched to nortriptyline, initiated at 12.5 mg/day and gradually increased up to 37.5 mg/day, without side effects.

To summarize, there is no contraindication to use TCAs in MG patients for treating neuropathic pain; however, caution should be undertaken and slow dose titration is advised. It may be advantageous to use TCAs with better anticholinergic adverse effect profile as desipramine or nortriptyline.

Gabapentin and Pregabalin

Gabapentin and pregabalin are antiepileptic agents approved for the treatment of several types of peripheral neuropathic pain. Both drugs act through similar mechanism, by inhibiting α2γ subunit of voltage-gated calcium channels. Gabapentin and pregabalin are used as first line agent for the treatment of neuropathic pain.

Effects on MG

A case report of MG aggravation during treatment with gabapentin was reported. The effect reversed upon withdrawal of gabapentin. Boneva and colleagues reported that MG was unmasked in a patient who received treatment with 400 mg/day of gabapentin. The presentation included ptosis, difficulties in chewing, and fatigue of speech. Following the case, administration of gabapentin was evaluated in an autoimmune experimental MG rat model. Clinical aggravation was observed following gabapentin administration in 70% of rats in the study. The authors suggested that caution should be exercised when considering the use of gabapentin in MG patients.

Pregabalin was not reported to aggravate or unmask MG; however, because the mechanism of action is similar to gabapentin and they share similar side effect profile, we would recommend exercising same caution when administering pregabalin to MG patient.

Carbamazepine

Carbamazepine is an antiepileptic agent widely used for several types of neuropathic pain, being the agent of choice in trigeminal neuralgia.

Effects on MG

Antibody-positive MG was reported after treatment with carbamazepine, supported with another case with suspected induction of MG by carbamazepine. A case report of two carbamazepine overdose incidences described patients presented with diffuse hypotonia and areflexia, suggesting that carbamazepine caused neuromuscular transmission defect. There is no formal precaution or contraindication to use carbamazepine in patients with MG; however, based on these findings, we would suggest weighing the risks of MG exacerbation before initiating carbamazepine therapy in MG patient.

Interactions

Carbamazepine is a potent inducer of several CYP450 isoenzymes, CYP450 3A4 in particular. Concomitant use of carbamazepine with cyclosporine or tacrolimus may result in increase in metabolism and reduced serum levels of cyclosporine and tacrolimus, therefore plasma levels of these drugs should be closely monitored.

Carbamazepine induces the metabolism of some corticosteroids. Although not reported
specifically for prednisone, a similar interaction could be expected. Corticosteroid efficacy should be monitored in patients receiving concomitant treatment with carbamazepine.

**Topiramate**

Topiramate is an antiepileptic agent, used widely for migraine prophylaxis, that has shown some efficacy in peripheral neuropathic pain.

**Effects on MG**

In a search that was conducted on September 17, 2008, in PubMed, EMBASE, and MEDLINE databases, we could not find negative association between topiramate and MG. On the other hand, we did not find literature on safe administration of topiramate in MG patient. We have treated an MG patient with topiramate up to 75 mg/day for 2 weeks (unpublished data). The therapy was discontinued because of ineffectiveness; topiramate did not precipitate any symptoms of otherwise controlled myasthenia. Because no evidence exist on aggravation of MG symptoms by topiramate, it seems reasonable to suggest that topiramate may be used in MG patients.

**Lidocaine**

Intravenous lidocaine was shown effective for the treatment of peripheral neuropathic pain, with its effect lasting beyond the presence of the drug in plasma in effective concentration. Topical lidocaine has been shown effective in focal peripheral neuropathic pain syndromes.

**Effects on MG**

Lidocaine may theoretically exacerbate MG as it inhibits the action of acetylcholine at the motor end plate.

We have administered intravenous lidocaine at a dose of 4 mg/kg (given as a 3-hour infusion) at three sessions to a myasthenic patient suffering from severe PHN unresponsive to standard treatments. There were no changes from baseline in the patient’s electrocardiogram and the patient did not complain on any adverse effects during lidocaine infusion or 60 minutes after it (unpublished data).

Topical lidocaine patches provide plasma concentration of lidocaine well below those that typically responsible for antiarrhythmic effects or toxicity and, theoretically, this mode of administration should be safer. However, some patients receive chronic treatment with topical lidocaine; therefore, the total exposure to lidocaine is prolonged. As specific data are lacking, we cannot draw conclusions about safety of intravenous or long-term topical lidocaine administration in MG patients.

**Interactions**

Lidocaine may prolong the QT interval, therefore caution should be undertaken when it is administered with tacrolimus, which has been associated with a possible risk for QT prolongation and/or torsades de pointes.

**Mexiletine**

Mexiletine, an oral analogue of lidocaine, is a Class IB antiarrhythmic, being used to treat neuropathic pain.

**Effect on MG**

Mexiletine has multiple side effects, among them muscle twitching and weakness, blurred vision, tremors, and speech difficulties, all these usually dose dependent. Therefore, in case clearly indicated, mexiletine should be used with great caution in MG patients, under close monitoring of side effects.

**Magnesium**

Intravenous magnesium has been implicated to reduce opioid requirements in postoperative pain and has been suggested to be effective in relieving headaches in patients with hypomagnesemia. Though a recent study failed to support the effectiveness of magnesium in acute headache, it is still used for its analgesic properties.

**Effect on MG**

Parenteral administration of magnesium have been reported to unmask MG in a previously asymptomatic patients or exacerbate muscle
weakness in myasthenic patients. Therefore, parenteral administration of magnesium sulfate is contraindicated in patients with MG.

**Benzodiazepines**

Benzodiazepines are used for treating skeletal muscle spasms and spasticity.

**Effects on MG**

Benzodiazepines are skeletal muscle relaxants and they may contribute to muscle weakness. Despite the report indicating that diazepam did not entail aggravation of the muscle weakness in a model of MG in rats, the safety of benzodiazepines in patients with MG is questionable. If the patient has primarily ocular symptoms, a small dose of benzodiazepine is acceptable; however, diplopia has been reported with benzodiazepines and attention must be paid on this adverse effect.

**Muscle Relaxants: Orphenadrine and Baclofen**

Orphenadrine is a muscle relaxant used for the treatment of spasticity and skeletal muscle spasms. Orphenadrine is contraindicated in MG patients (Prescribing Information Norflex 2007), as it may exacerbate muscle weakness in these patients.

Baclofen is a derivative of γ-aminobutyric acid (GABA) and acts specifically at the spinal end of the upper motor neurons to cause muscle relaxation. Systemic or intrathecal administration of baclofen is useful in the treatment of muscular spasm due to conditions such as multiple sclerosis and spasticity of spinal cord origin.

**Effects on MG**

Asthenia is one of the most commonly reported CNS effects with baclofen (5% to 15%) (Prescribing Information Baclofen Oral Tablets, 2001; Prescribing Information Lioresal Intrathecal Injection), though there are no data on higher incidence in MG patients. Baclofen is not contraindicated in MG; however, as the clinical impact of asthenia in MG patient may be substantial, baclofen should be used with caution in these patients.

**Regional Anesthesia With Local Anesthetics**

There is no definitive clinical evidence that MG patients are more sensitive to local anesthetics than are normal patients. Nevertheless, it would seem obvious that the disease should predispose to increased weakness in MG patients. Local anesthetics decrease the sensitivity of the postsynaptic membrane to acetylcholine. This theoretically could cause weakness in myasthenics if blood concentrations are high enough. Ester anesthetics, which are metabolized by cholinesterases (e.g., 2-chloroprocaine, procaine, cocaine, and tetracaine) may present particular problems in patients taking AChE inhibitors. The amide local anesthetics (e.g., ropivacaine, mepivacaine, lidocaine, bupivacaine, xylocaine) might theoretically be better choices because they are cleared by hepatic metabolism and not hydrolyzed by serum cholinesterases.

Regional and local anesthesia should be performed using reduced doses of amide (rather than ester) local anesthetics to avoid high blood levels. Traditionally, blockade of the innervation of intercostal muscles is avoided to minimize the risk of respiratory muscle weakness. However, the safe and successful use of thoracic epidural blockade with bupivacaine for intraoperative and postoperative analgesia for transsternal thymectomy has been reported.

**CONCLUSIONS**

MG-related symptoms may be aggravated by several factors such as emotional upset, elevated temperatures and certain drugs. When choosing a specific drug for pain management in MG patient, the clinician should be aware of possible impact of the analgesic treatment on the disease course and symptoms of MG, as well as consider the possible drug-drug interactions with the multiple agents used to treat MG. Table 1 summarizes the available data regarding these issues. In case the patient undergoes plasmapheresis, its impact on the pharmacokinetics of analgesic agents should be considered to adjust the dosage, in case plasmapheresis removes the drug from plasma.
NSAIDs, acetaminophen (paracetamol), and dipyrone appear to be safe in MG, though the interactions with corticosteroids and cyclosporine should be considered.

Systemic opioids may be used, though doses should be increased gradually to avoid respiratory depression. A potential drug interaction exists between cyclosporine and opioids that are substrates of CYP450 3A4 or P-gp. When MG patient is treated with cyclosporine, these opioids should be used with greater caution and opioid-related adverse effects should be monitored more closely.

TCAs may interfere with neuromuscular transmission under experimental conditions, therefore should be used with caution in patients with MG. If one decides to use TCAs in myasthenic patient, we would suggest to start with lower doses of TCA with safer anticholinergic adverse effect profile and make dose increments in a more moderate manner.

Gabapentin and carbamazepine has been reported to aggravate MG; therefore, this risk should be weighted against the possible benefit when treating neuropathic pain. Pregabalin and gabapentin have similar mechanism of action and adverse effect profile; therefore, we believe practicing the same cautions with pregabalin is reasonable.

Several drugs are known to cause muscle weakness and should be used with caution in MG. Though the adverse effects as generalized weakness or asthenia are clinically distinguishable from MG-specific local muscle weakness, the impact of weakness may be more substantial in MG patients than in general population. These drugs include duloxetine, valproic acid, systemic local anesthetics, and mexiletine, as well as muscle relaxant benzodiazepines and baclofen. Orphenadrine and intravenous magnesium are contraindicated in MG, therefore should not be used. Topiramate and triptans appear to be safe in MG and can be used for treating migraine.

It is important to note that most of the aforementioned agents reported to unmask or aggravate MG do not cause irreversible damage to the patients, and the symptoms are usually reversible with the discontinuation of the offending drug. Therefore, if clearly indicated, they may be initiated at low doses and increased gradually until achieving desired response or undesired side effects.

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