Acetylcholinesterase Inhibitors in MG: to be or not to be?

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CME Information
Product: JR20 - Acetylcholinesterase Inhibitors in MG: to be or not to be?

Course Description
Myasthenia gravis (MG) is an autoimmune disorder usually caused by antibodies against either the acetylcholine receptor (AChR) or muscle-specific tyrosine kinase (MuSK) at the neuromuscular junction. Neuromuscular transmission failure results in muscle fatigue and weakness that can be treated symptomatically with acetylcholinesterase inhibitors (AChEIs). Long-term treatment with nonselective AChEIs may have considerable drawbacks; thus, this medication is ideally tapered when strength improves. Patients with AChR antibodies respond beneficially to treatment, whereas patients with MuSK antibodies generally do not. Recently, the selective AChEi EN101, which specifically targets the isoform of read-through AChE (AChE-R), has been developed and may be of importance for symptomatic relief in AChR-antibody seropositive MG. This article is a review of the mechanisms, therapeutic effects, and drawbacks, with both old and new AChEIs in MG.

Intended Audience
This course is intended for Neurologists, Physiatrists, and others who practice neuromuscular, musculoskeletal, and electrodiagnostic medicine with the intent to improve the quality of medical care to patients with muscle and nerve disorders.

Learning Objectives
Upon conclusion of this program, participants should be able to:

1. discuss symptomatic management of myasthenia gravis (MG) with acetylcholinesterase inhibitors (AChEIs).
2. recognize electrophysiologic factors that affect response to acetylcholinesterase inhibitors treatment of myasthenia gravis.
3. describe new developments relevant to the treatment of myasthenia gravis with acetylcholinesterase inhibitors.

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ABSTRACT: Myasthenia gravis (MG) is an autoimmune disorder usually caused by antibodies against either the acetylcholine receptor (AChR) or muscle-specific tyrosine kinase (MuSK) at the neuromuscular junction. Neuromuscular transmission failure results in muscle fatigue and weakness that can be treated symptomatically with acetylcholinesterase inhibitors (AChEIs). Long-term treatment with nonselective AChEIs may have considerable drawbacks; thus, this medication is ideally tapered when strength improves. Patients with AChR antibodies respond beneficially to treatment, whereas patients with MuSK antibodies generally do not. Recently, the selective AChEI EN101, which specifically targets the isoform of “read-through” AChE (AChE-R), has been developed and may be of importance for symptomatic relief in AChR-antibody seropositive MG. This article is a review of the mechanisms, therapeutic effects, and drawbacks, with both old and new AChEIs in MG.


ACETYLCHOLINESTERASE INHIBITORS IN MYASTHENIA GRAVIS: TO BE OR NOT TO BE?

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Acquired myasthenia gravis (MG) is an autoimmune neuromuscular disorder that causes fluctuating skeletal muscle weakness. MG is often divided into an ocular form, affecting the extraocular muscles, and a generalized form that also affects bulbar, facial, neck, and limb muscles. The annual incidence of MG has been reported to be about 3–4 cases per million, and the prevalence is about 60 cases per million.1,26,39 Higher rates have been reported in the USA, with current estimates indicating a prevalence as high as 20 per 100,000.28 In 80%–85% and 55% of patients with generalized MG and ocular MG, respectively, antibodies against the nicotinic acetylcholine receptor (AChR-Abs) have been detected.21,43 In 1976 it was found that immunization with AChR in rabbits produced clinical and neurophysiological signs of MG.11 Antibodies against the AChR impair function primarily by three mechanisms: (1) blocking of the ACh-binding site; (2) cross-linking of the AChRs on the postsynaptic membrane; and (3) complement activation, resulting in destruction of the postsynaptic muscle membrane.8

Among patients who lack AChR-Abs, ~70% have serum antibodies against the muscle-specific tyrosine kinase (MuSK).13 However, recent reports have also found MuSK-Abs in a small fraction of patients who are seropositive for AChR-Abs.31 In animal models, MuSK-Abs are capable of reducing AChR clustering and thereby impairing neuromuscular transmission.36 Treatment of MG can be divided into symptomatic and immunosuppressive, disease-modulating treatment. This review deals only with symptomatic treatment with the acetylcholinesterase inhibitors (AChEIs).

Historic Aspects of AChEIs in MG. AChEIs prevent the breakdown of circulating ACh at the neuromuscular junction, which provides short-term relief of muscle weakness by improving neuromuscular transmission. In 1934 Mary Walker, a young resident in St. Alfege’s hospital near London, thought that it would be worthwhile to try physostigmine, a partial anticholinesterase, as treatment for a patient with MG based on the resemblance of curare intoxication and MG.31 Injection of physostigmine resulted in alleviation of the ptosis, and thus neostigmine (Prostigmine), which could be given both orally and paren-
terally, brought about a revolution in the treatment of MG. In 1952 a very short-acting AChEI, edrophonium (Tensilon), was introduced primarily for diagnostic testing. In 1954 pyridostigmine bromide (PB; Mestinon), and in 1955 ambenonium chloride (Mytelase), both with longer actions than prostigmine and with fewer muscarinic side effects, were made available.27,34

Nonselective AChEIs: Current Clinical and Electrophysiological Aspects. The nonselective AChEIs interfere with the catalytic breakdown of ACh, making neurotransmitters available for a longer period of time at the nicotinic AChRs (nAChRs) at the neuromuscular junction. The most common form of AChEI is PB, which is especially useful at the onset of MG. In some patients, typically those with purely ocular weakness, this treatment may be sufficient to manage paresis and fatigability. The usual starting dose of PB is 60 mg every 4–6 h, and the recommended maximum dose is 120 mg every 3 h.32 Overdose of PB can cause cholinergic crisis, which is characterized by increasing muscle weakness that sometimes results in dysphagia and respiratory insufficiency. The distinction between a cholinergic and a myasthenic crisis, the latter being caused by myasthenic weakness, is of utmost importance for the medical care of the patient. These two conditions have different clinical reactions related to the initial intake of the drug. During incipient overdose, symptoms of weakness increase shortly after ingestion and wane before the next dose, a situation opposite to that seen in myasthenic crisis. This typical pattern may not always be easy to detect; therefore, other markers are useful. For example, extra discharges (EDs) occurring after the compound motor action potential (CMAP) on motor nerve stimulation are sometimes observed in MG patients who are receiving high doses of PB and may signify impending cholinergic crisis.42 A recent study revealed that patients with EDs were more prone to have daily nicotinic side effects, including muscle fasciculations and fatigue [8 out of 22 patients (36%)], as a possible sign of overtreatment.30 In this study, elderly MG patients were more prone to develop cholinergic side effects, as well as EDs. Additionally, MG patients who are seropositive for MuSK-Abs (MuSK+) often have a negative edrophonium test and are also reported to clinically benefit less from PB. Instead, MuSK+ patients may actually worsen or even develop muscle cramps and fasciculations in response to PB treatment.9,29 EDs with low-frequency motor nerve stimulation have been described in MuSK+ MG patients on AChEI treatment, indicating an abnormal sensitivity to ACh.29 This abnormal ACh sensitivity may reflect the disruption of the normal endplate receptor morphology, which is due to reduced AChR clustering.44

AChEIs not only affect the nAChRs but also the muscarinic receptors (mAChRs) in the parasympathetic system. Common muscarinic adverse effects include increased gut motility, which may lead to stomach pain and diarrhea, increased gastric acid secretion, hyperhidrosis, salivation, and lacrimation. The presence of daily muscarinic adverse effects has been shown to correlate with the baseline inhibition of AChE activity in the blood of patients on regular AChEI medication.30

Neurophysiology and AChEIs. After an intravenous injection of edrophonium, single-fiber electromyography (SFEMG) examination in a normal muscle reveals unchanged jitter. In an abnormal potential pair, as in an MG patient, the degree of impulse blocking decreases or disappears, and the jitter tends to return to a normal value. If the patient is already receiving AChEI treatment, the reverse edrophonium effect, namely, increased jitter and more frequent blockings, is observed in a muscle that otherwise responds positively to the drug.37 This is assumed to reflect the variation among motor endplates with regard to receptor blockade and effectiveness of treatment. For example, individual endplates may be overtreated even if the entire muscle does not exhibit overtreatment. However, PB treatment in MG is not totally harmless. Animal studies in the 1970s revealed both morphologic and physiologic abnormalities at the neuromuscular junction associated with the use of AChEIs, such as degeneration of the postsynaptic folds in endplates situated on red, or slow, muscle fibers.7,15,40 Presynaptic changes are also possible effects of PB treatment, since SFEMG studies of MG patients on regular PB treatment showed increased fiber density as a sign of reinnervation after denervation.12

Isoforms of AChE and Cholinergic Imbalance. The isoforms of mammalian AChE include the “synaptic” (AChE-S) isoform which is bound to the muscle basement membrane, an “erythropoietic” (AChE-E) isoform, and the rare stress-related “read-through” acetylcholinesterase variant (AChE-R).3,22 AChE-S is specialized for the rapid hydrolysis of ACh at the neuromuscular synapse, while the soluble AChE-R is specialized for nonsynaptic hydrolysis and morphogenesis.5,35 Abnormal cholinergic neurotransmission, including chronic AChE blockade and acute stress, triggers the overexpression of the normally
rare AChE-R variant. Continued accumulation of AChE-R may be detrimental, since it prolongs the state of cholinergic impairment and increases noncatalytic activities of AChE. Nonselective cholinesterase inhibition and overexpressed AChR-R in transgenic mice has been shown to cause severely myopathic muscle changes (atrophic and vacuolated muscles), denervation-reinnervation characterized by increased axon branching, as well as increased density of small immature motor endplates. An elevation of AChE-R is noted in the serum of patients with AChR-Ab seropositive MG without treatment and in rodents with experimental autoimmune myasthenia gravis (EAMG). PB and other nondiscriminative AChEIs can transiently compensate for the reduced numbers of AChRs at the neuromuscular junction, although they induce AChE-R overproduction. This overproduction would limit the duration of AChEI capacity to retrieve stable CMAP and intensify the disease-associated cholinergic imbalance, reaffirming the detrimental effect of long-term nonselective AChEI treatment in MG.

**Novel Selective AChEIs.** EN101 is an antisense oligodeoxynucleotide that acts at the mRNA level and selectively reduces the production of the enzymatic isoform of AChE-R through destruction of AChE-R mRNA. This compound selectively lowers the levels of AChE-R in both blood and muscle yet leaves the synaptic variant of ACh-E-S unaffected. EN101 has been tested in rats with EAMG, in which daily oral or intravenous administration of EN101 reduces AChE in blood and muscle and improves survival, muscle strength and disease severity. Also observed was a stabilization of the CMAP decrement on RNS and muscle strength over the entire course of treatment. This effect is comparable to that of PB, which wears off within hours, causing pronounced fluctuations in muscle strength. In another study of EAMG, rats receiving treatment with EN101, stimulated SFEMG showed improvement of abnormal fiber pairs [both jitter measured as the mean consecutive difference (MCD) and blockings] for 24 h. In comparison, intraperitoneal administration of PB resulted in reduced jitter and blockings for only 2 h. It was also found that clinical and electrophysiological amelioration was associated with reduction in the autoimmune responses.

A Phase 1b open-label trial with oral EN101 (Monarsen) was recently conducted in 16 patients with stable MG who were receiving at least 180 mg of PB daily. Clinically, the overall mean change in quantitative myasthenia gravis score from baseline was 6, resulting in a significant mean improvement of 46.5%. Additionally, the swallowing time component was improved. The effects of EN101 lasted for over 24 h, indicating the possibility of a reduction in multiple dosing through the use of antisense therapy. Dryness of mouth and eyes were the only reported adverse effects. However, the observation time was limited to 1 month, making placebo effects difficult to exclude, even with the objective sign of improved ptosis. It was unclear if any MuSK+ patients were included in this study.

**AChEIs as Future Immunomodulators?** In addition to direct esterase inhibition, another potential role for AChEIs is to mediate antiinflammatory responses through cholinergic upregulation. Immune cells, as well as the nervous system, possess a complete cholinergic system consisting of ACh, mAChRs, and nAChRs, choline acetyltransferase (ChAT) and AChE. The nervous system produces large amounts of ACh, and, thus, the immune cholinergic system can mediate neuroimmune interactions. Cytokines are major mediators of inflammation, and in MG, TNF-α and IL-1β play an important role for the autoimmune response. Antiinflammatory effects are mediated through stimulation of the α7 nAChRs located on lymphocytes, resulting in inhibition of lymphocyte proliferation and reduced secretion of these cytokines. Reduction of extracellular AChE activity is achieved both by edrophonium (90%–95% inhibition) and EN101 (20%–25%), rendering more ACh available for nAChR stimulation. On the contrary, excess cholinergic upregulation may result in binding of ACh to mAChR, which instead enhances proliferation and activation of lymphocytes.

In conclusion, it is important to tailor the treatment individually for each patient with MG. Since different muscles are affected to varying degrees, the effect of treatment must be optimized for vital muscles. Ideally, since nonselective AChEIs are most effective at the onset of MG, the dosage of AChEIs is ideally tapered as strength improves with immunosuppressive treatment. The decrease in efficiency with increasing time is likely related to the increased levels of the AChE-R isoform, which may cause the morphologic and physiologic abnormalities at the neuromuscular junction that were originally observed in the 1970s in animals treated with AChEIs. The reported inefficiency of AChEIs in MuSK+ patients suggests that the disrupted endplate morphology with reduced AChR clustering may be responsible for the poor outcome. In patients where overdose of AChEIs is suspected, the presence of EDs on electrical nerve stimulation may assist diag-
nosis, since EDs are related to nicotinic side effects. In cases where EDs are found, the question of possible overdose of PB should be addressed. The novel selective AChE-R inhibitor EN101 is promising as a symptomatic medication in AChRAb seropositive MG and may possess the potential to downregulate the autoimmune response, although this has yet to be proven.

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**REFERENCES**