Off-Label Drug Uses

Pyridostigmine: Postpoliomyelitis Syndrome

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This *Hospital Pharmacy* feature is extracted from *Off-Label Drug Facts*, a publication available from Wolters Kluwer Health. *Off-Label Drug Facts* is a practitioner-oriented resource for information about specific drug uses that are unapproved by the US Food and Drug Administration. This new guide to the literature enables the health care professional or clinician to quickly identify published studies on off-label uses and determine if a specific use is rational in a patient care scenario. References direct the reader to the full literature for more comprehensive information before patient care decisions are made. Direct questions or comments regarding *Off-Label Drug Uses* to jgeneral@ku.edu.

THERAPY CONSIDERATIONS

Evidence from controlled studies and meta-analyses evaluating pyridostigmine for treatment of postpoliomyelitis syndrome have demonstrated no benefit for fatigue, muscle strength or function, and pain when compared to placebo. In a small noncontrolled trial, some patients experienced improvement in fatigue during treatment with the drug.

European Federation of Neurological Societies consensus guidelines on the management of postpoliomyelitis syndrome state that this agent is not effective in the management of fatigue and muscular weakness in postpoliomyelitis syndrome.

RATIONALE

Postpoliomyelitis syndrome is characterized by the onset of new and progressive muscular fatigue, general fatigue, pain, muscle weakness, and atrophy. Although the exact incidence has not been established, symptoms occur decades after recovery from acute polio.^{1–3} Pyridostigmine, an anticholinesterase agent, inhibits the hydrolysis of acetylcholine, prolonging its effects in the neuromuscular junction. Studies suggest that neuromuscular junction transmission in postpoliomyelitis syndrome may improve with anticholinesterases.⁴

POPULATION

Adults with postpoliomyelitis syndrome.

DISCUSSION

Guidelines

European Federation of Neurological Societies

The European Federation of Neurological Societies consensus guidelines on the diagnosis and management of postpoliomyelitis syndrome reviewed 2 controlled trials and 2 open trials evaluating pyridostigmine for the management of muscular strength, fatigue, and quality of life. Positive benefits observed in fatigue in noncontrolled trials were not confirmed in controlled trials. Though one trial reported improvement in walking, it was not accompanied by a significant improvement in muscle strength. Based on these studies, the guidelines state that pyridostigmine is not effective in the management of fatigue and muscular weakness in postpoliomyelitis syndrome. Steroids and amantadine were also cited as not providing therapeutic effect.¹

Controlled Trial

In a double-blind, placebo-controlled, multicenter trial, 126 adult patients with postpoliomyelitis syndrome and new symptoms of general or muscular fatigue and new weakness of at least 1 year duration were randomized to receive pyridostigmine or placebo for 6 months. The dose was initiated at 30 mg daily and gradually increased by 30 mg every other day over an 11-day period to a target dose of 60 mg

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3 times daily. Mean ages were 56.8 and 55.7 years for the pyridostigmine and placebo groups, respectively. There was no significant difference between the 2 groups for mean age at acute polio (9.5 vs 7.5 years). Primary endpoints included the difference between assessments at baseline and 6 months of treatment for the physical functioning scale score via the Short-Form Health Survey-36, which assesses 8 quality of life parameters (eg, physical functioning, physical role, bodily pain, general health, vitality, social functioning, emotional role, mental health). A higher score indicates a better quality of life, with each of the parameters scored between 0 and 100. Other endpoints included assessment of isometric muscle strength (in 12 muscle groups in each patient), fatigue (via the Fatigue Severity Scale), and insulin-like growth factor-1 (IGF-1) serum levels. All patients completed the trial. In a primary intent-to-treat analysis, there were no significant differences in changes from baseline to 6 months between the pyridostigmine and placebo groups for quality of life, isometric strength, fatigue, and IGF-1 serum levels. A nonsignificant improvement of isometric strength was observed in the very weak muscles at 6 months of treatment in the pyridostigmine group.⁴

In a double-blinded, placebo-controlled trial, 67 adult patients with postpoliomyelitis syndrome with specific criteria for symptoms for fatigue, muscle dysfunction and strength, and neurotransmitter transmission defects were randomized to receive either pyridostigmine ($n = 34$) or placebo ($n = 33$) 4 times daily for 14 weeks. The pyridostigmine dose was gradually increased from 10 mg 4 times daily to 60 mg 4 times daily over the first 6 days of the trial. On day 4, atropine (0.125 mg daily) was added to mask pyridostigmine parasympathetic effects. Patients in the placebo group received pyridostigmine dosing for the first 3 days in the same incremental manner and tapered over 2 days. Placebo was administered from day 6 to the end of the trial. The placebo group also received placebo atropine starting on day 4. The primary outcome was assessment of "energy" via the Nottingham Health Profile score (NHP_E; 0 = no complaints; 100 = answered yes to all questions). Secondary outcomes included assessment of fatigue, physical performance (eg, 2-minute walking distance, duration of walking), and muscular function (eg, maximum quadriceps strength, maximum voluntary activation [MVA], muscle fatigability, and neuromuscular transmission defects-jitter). A total of 31 subjects in each group completed the trial and were included in the outcome analysis. Though both

groups demonstrated significant improvement in energy levels and fatigue from baseline values, there was no difference in the degree of change for these assessments between the 2 groups. When compared to placebo, the pyridostigmine improved the 2-minute walking distance by 7.2 meters (6%; $p = .003$). Though pyridostigmine significantly improved maximum walking performance and duration of walking from baseline, there were no differences in the degree of change for these parameters between the 2 groups. Though both groups showed significant improvements in quadriceps strength, there was no difference in change between the 2 groups. No differences in change between the 2 groups were noted for MVA, muscle fatigability, or jitter. The authors concluded that the results of this study demonstrated a lack of benefit with the use of pyridostigmine for reducing fatigue. The use of this agent for improving muscle function is not established; although some improvements were noted in walking distance, these changes were not clinically relevant.⁵

Noncontrolled Trial

In an open trial, 27 adult patients with postpoliomyelitis syndrome with generalized fatigue and muscle fatigability received pyridostigmine. The initial dosage of 30 mg every day was increased by 30 mg every other day to a maximum dose of 60 mg 3 times daily. Responders were defined as those experiencing an improvement of at least 20% on initial fatigue scores. Two patients were unable to tolerate the drug. Of the 25 remaining patients, 64% (16) reported a mean improvement of 56% on the Hare Fatigue Symptom Scale score. Of these responders, 3 patients also experienced improvement in activities of daily living and 2 improved on mobility indices. Mean duration of treatment was 1.2 years in responders (range, 0.1 to 2.8 years). Of the 11 patients who did not respond, 2 developed increased weakness, which reversed upon discontinuation of the drug.⁶

Meta-analyses

A Cochrane review evaluated 2 placebo-controlled trials evaluating the effects of pyridostigmine on fatigue and muscle endurance or function. Meta-analyses of fatigue results from both trials demonstrated that there was no difference between the 2 groups for effect on fatigue as measured by FSS (mean difference [MD], -0.06; 95% CI, -0.34 to 0.21), via the Hare Fatigue Symptom Scale (MD, 0.07; 95% CI, -0.71 to 0.31), or via the energy category of the NHP_E scale (MD, 1.10; 95% CI, -16.24 to 18.44).

In addition, both studies did not show a difference in change for muscle strength between the 2 groups for very weak muscles (MD, 33.90; 95% CI, -5.49 to 73.29), weak muscles (MD, -1.80; 95% CI, -11.75 to 8.15), and relatively strong muscles (MD, -0.30; 95% CI, -4.22 to 3.62). No benefit was also noted for activity limitations or pain. The medication caused adverse events in a substantial number of patients receiving the drug. The review concluded that moderate quality evidence demonstrated no beneficial effect for use of pyridostigmine in a fixed dose of 180 mg or 240 mg daily. Because higher doses (540 mg to 740 mg daily) are used to treat muscle weakness in myasthenia gravis and because there is interpatient variability in plasma concentrations, it is suggested that higher doses or individually adjusted doses may need further evaluation for the management of symptoms of postpoliomyelitis syndrome.³

RISK/BENEFIT CONSIDERATIONS

This is a limited safety profile. Refer to package labeling for complete prescribing information (eg, Warnings/Precautions, Adverse Reactions, Drug Interactions).

In a controlled trial, 3 severe adverse events occurred with pyridostigmine (palpitations with dizziness, sepsis secondary to diverticulitis, and ductal

carcinoma of the breast). The most commonly cited adverse events in the pyridostigmine group were gastrointestinal, including diarrhea/loose stools (55%) or nausea/vomiting/stomach upset (28%).⁴ Other adverse events included muscle cramps, blurred vision, and increased urinary frequency.⁶

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