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RESEARCH ARTICLE

Preliminary Observations from Acetylcholine Esterase Inhibition in Symptomatic Orthostatic Hypotension of Parkinson's Disease

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ABSTRACT. *Acetylcholine esterase inhibition with pyridostigmine has been widely used for orthostatic hypotension (OH). However, its role in patients with OH secondary to parkinsonism has not been reported. In this report we present our center's experience on the use of pyridostigmine in OH of Parkinson's disease. We reviewed charts of 300 patients seen at the University of Toledo Syncope and Autonomic Disorders Center from 2003 to 2010 and found 20 patients (14 males, 70%), aged 50–85 years (mean 67 years), eligible for inclusion in this study. Patients were included in this study if they had a known diagnosis of Parkinson's disease and reported clinical symptoms and head-up tilt table test features suggestive of OH. In each patient pyridostigmine was used as an add-on therapy. The mean duration of follow-up was 9±3 months. Nineteen patients tolerated pyridostigmine through dose titration. Fourteen patients reported subjective improvement in their orthostatic symptoms following initiation of pyridostigmine therapy. Of these, 12 patients reported subjective improvement in the frequency and severity of their symptoms, and in two patients symptoms of orthostatic intolerance were completely abolished. Six patients however reported no improvement in their symptoms (including all of the patients with the Levy body variant form). Pyridostigmine use was also associated with improvement in standing heart rate (98 at baseline, 86 at 3 months and 72 at 6 month and systolic blood pressure (95 mmHg at baseline, 105 mmHg at 3 and 6 months). Pyridostigmine improves heart rate and standing systolic blood pressure in patients with idiopathic Parkinson's disease, which results in improvement of the symptoms of OH.*

KEYWORDS. *Acetylcholine esterase inhibition, pyridostigmine, Parkinson's disease.*

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Introduction

Orthostatic hypotension (OH) is a common clinical problem that principally affects the older population. The last decade has witnessed a substantial increase in our understanding of this clinical condition, and we now know that there are multiple causes for this finding. One of the secondary causes of OH that can commonly be seen in the elderly population is parkinsonism.[1–4] Almost, 60% of the patients with parkinsonism demonstrate an orthostatic fall in blood pressure of 20 mmHg on standing, but only 20% of these patients suffer from symptoms related to orthostatic hypotension.[4] There have been few studies that have evaluated the use of medications to treat symptomatic OH in patients with Parkinson's disease.

Pyridostigmine, a peripheral acetylcholinesterase inhibitor, is a novel treatment option for patients suffering

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from postural tachycardia syndrome (POTS), presumably acting through facilitation of ganglionic and neural transmission in both the sympathetic and parasympathetic nerves.[5,6] This augmented baroreceptor sensitivity that occurs with pyridostigmine has been shown to have a beneficial role in patients suffering from neurogenic orthostatic hypotension (NOH).[7–9]

In this article we present our center's experience in the management of OH with pyridostigmine in a subgroup of patients who suffer from Parkinson's disease.

Methods

The study was a retrospective study approved by our Institutional Review Board. We screened 300 dysautonomia patients who were being followed at our institution's Syncope and Autonomic Disorders Center for various dysautonomias. A total of 20 patients were found to be eligible for inclusion in the current study. All of the patients had a diagnosis of parkinsonism and had developed symptoms suggestive of OH.

Criterion for diagnosis of parkinsonism

The diagnosis of Parkinson's was made by a neurologist specializing in Parkinson's disease using standard diagnostic criteria.[10]

Criterion for OH

A consensus definition of OH was used for inclusion of patients in this retrospective study. Patients were included if they had a reduction of at least 20 mmHg in systolic blood pressure or a 10 mmHg reduction in diastolic blood pressure within 3 min of assuming upright posture or using a standard head-up tilt table test (HUTT). The details of our HUTT protocol can be found elsewhere.[11,12]

All these patients had initially been treated with a series of medications that included fludrocortisone, midodrine, and methylphenidate prescribed by their primary neurologists. These patients continued to experience debilitating symptoms of OH and were referred to our center for a second opinion. They were initiated on a series of second-line therapies starting with pyridostigmine and progressing to octreotide or erythropoietin if necessary.

The response to the therapy was assessed from the subjective improvement in the patient's symptoms as well as the improvement in their orthostatic blood pressure parameters.

The information about the current symptoms, side effects of medications, and overall improvement in symptoms from each patient was collected from the patient's charts, physician communications, and direct patient inquiry. We also collected information about prior trials of various medications before initiation of pyridostigmine; however, that information was not available for some of the patients. A treatment was considered successful if the patient reported symptomatic relief and if the hemodynamic parameters showed improvement compared with previous readings. Heart rate and blood pressure were recorded in supine, sitting, and standing positions and after 3 min of standing during each visit.

Results

Twenty patients, 14 males (70%), aged 50–85 years (mean 67 years), were included in this retrospective analysis. All patients were suffering from parkinsonism and were sent to our center for management of OH symptoms. Each of these patients was experiencing symptoms of orthostatic dizziness and presyncope. Thirteen (65%) had experienced frank syncope.

Clinical course of parkinsonism

The mean duration from the diagnosis of parkinsonism to the onset of OH hypotension was 28 months (range 18–38 months). Seventeen patients were diagnosed as having the idiopathic (common) variant of parkinsonism (12 males, 5 females), whereas three patients (2 males, 1 female) were felt to be suffering from the Levy body disease variant.

Pyridostigmine use

In each patient pyridostigmine was used as an add-on therapy. All patients were initially started on pyridostigmine 30 mg orally twice daily. After a period of 1 week, if no therapeutic effect was noted and if the drug was tolerated, the dose was increased to 60 mg orally three times daily. After a 2-week interval if the drug was tolerated but no therapeutic benefit was noted the dose was increased to a maximum of 90 mg orally three times daily or changed to 180 mg of the sustained release form once daily.

The mean duration of follow-up was 9 ± 3 months (range 6–12 months, median 7 months). Nineteen patients tolerated pyridostigmine through dose titration. One patient at a dose of 90 mg orally three times daily did not tolerate the drug due to nausea and diarrhea.

Effects on subjective improvement

Fourteen patients reported subjective improvement in their orthostatic symptoms following initiation of pyridostigmine therapy. Of these, 12 patients reported subjective improvement in the frequency and severity of their symptoms; in two patients symptoms of orthostatic intolerance were completely abolished. Six patients however reported no improvement in their symptoms (including all of the patients with the Lewy body variant form). Because of the refractory nature of the symptoms of orthostatic intolerance, these six patients were subsequently treated with either octreotide or erythropoietin. Three out of these six patients (all males) reported subjective improvement (one with octreotide and two

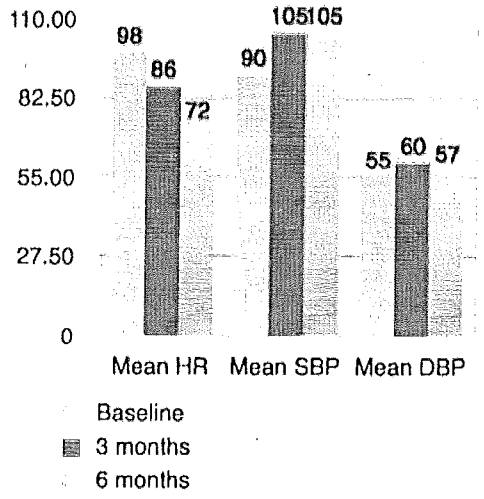

Figure 1: Effect of pyridostigmine on mean standing heart rate, mean standing systolic blood pressure, and mean standing diastolic blood pressure. Of note, pyridostigmine use was associated with improvement in standing heart rate and systolic blood pressure.

with erythropoietin); the other three continue to suffer from symptoms of OH despite all attempts at treatment.

Effects on hemodynamic parameters

Figure 1 demonstrates the effect of pyridostigmine on mean standing heart rate, mean standing blood pressure, and mean standing diastolic blood pressure. Pyridostigmine use was associated with marked improvement in the standing heart rate and a modest improvement of standing systolic blood pressure.

Discussion

Pyridostigmine is a reversible, peripheral cholinesterase inhibitor, which increases the availability of acetylcholine at preganglionic nicotinic receptors (both sympathetic and parasympathetic) and muscarinic receptors (postganglionic parasympathetic). This leads to enhanced neural transmission, which improves baroreceptor reflex functions.[5,6] This augmented baroreceptor sensitivity that occurs with pyridostigmine has been shown to have a beneficial role in patients suffering from NOH.[7] In one open-label study and one placebo-controlled study using pyridostigmine there was reported to be a statistically significant improvement in standing diastolic blood pressure in patients with NOH.[8] Further improvement in patient satisfaction using the CASS questionnaire was also seen following chronic pyridostigmine therapy. In an open-label study 20 out of 28 patients with NOH receiving pyridostigmine reported marked improvement (using the CASS questionnaire) at 19 ± 8.9 months of follow-up.[9]

In our current study we demonstrated that pyridostigmine use was associated with a modest improvement in the symptoms of orthostatic hypotension. However, interestingly, only patients having the idiopathic variant of parkinsonism demonstrated a response to the medication. All patients with the Levy body variant of parkinsonism did not benefit from pyridostigmine therapy. Although this study could not explain this discrepancy, the more aggressive nature of the Levy body disease variant (with widespread neuronal degeneration) compared with idiopathic parkinsonism could be a contributing factor.

The clinical improvement in symptoms of patients in our study was associated with an improvement in both standing heart rate and systolic blood pressure. Pyridostigmine has been demonstrated to improve vasomotor tone. Singer et al[8] in a double-blinded, placebo-controlled crossover study in 58 patients with neurogenic hypotension showed that the use of pyridostigmine with iodine was associated with improvement in standing diastolic blood pressure without any supine hypertension. Also pyridostigmine use is associated with improvement in the cardiovagal tone and this effect is responsible for improvement in the standing heart rate, which has been demonstrated in patients with postural orthostatic tachycardia syndrome[13,14] as well as in patients with congestive heart failure.[15]

Limitations

The results of this study are encouraging as they may lay a foundation for subsequent larger randomized controlled studies to help answer many of the questions which this limited study could not. Having said that, there are certain important limitations in the design of the current study. The study group itself was quite small, and it was not a randomized controlled trial. Rather, each patient was used as his or her own control. Also, our study lacked a standardized criterion for evaluating efficacy of therapy. In addition, the assessment of hemodynamic responses was not standardized. All patients presented here were suffering from unusually severe and refractory forms of OH secondary to parkinsonism and therefore may not represent the majority of patients with OH in the general population.

Conclusion

Pyridostigmine use in patients with OH secondary to idiopathic parkinsonism is associated with modest improvement in standing heart rate and standing systolic blood pressure, which further results in subjective improvement in the symptoms of OH.

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