Pyridostigmine in the Treatment of Postural Orthostatic Tachycardia: A Single-Center Experience

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Background: *The long-term efficacy of pyridostigmine, a reversible acetyl cholinesterase inhibitor, in the treatment of postural orthostatic tachycardia syndrome (POTS) patients remains unclear. We report our retrospective, single-center, long-term experience regarding the efficacy and adverse effect profile of pyridostigmine in the treatment of POTS patients.*

Methods: *This retrospective study included an extensive review of electronic charts and data collection in regards to patient demographics, orthostatic parameters, side-effect profile, subjective response to therapy, as well as laboratory studies recorded at each follow-up visit to our institution's Syncope and Autonomic Disorders Center. The response to pyridostigmine therapy was considered successful if patient had both symptom relief in addition to an objective response in orthostatic hemodynamic parameters (heart rate [HR] and blood pressure). Three hundred patients with POTS were screened for evaluation in this study. Of these 300, 203 patients with POTS who received pyridostigmine therapy were reviewed. Of these 203 patients, 168 were able to tolerate the medication after careful dose titration. The mean follow-up duration in this group of patients was 12 ± 3 (9–15) months. Pyridostigmine improved symptoms of orthostatic intolerance in 88 of 203 (43%) of total patients or 88 of 172 (51%) who were able to tolerate the drug. The symptoms that improved the most included fatigue (55%), palpitations (60%), presyncope (60%), and syncope (48%). Symptom reduction correlated with a statistically significant improvement in upright HR and diastolic blood pressure after treatment with pyridostigmine as compared to their baseline hemodynamic parameters (standing HR 94 ± 19 vs 82 ± 16, $P < 0.003$, standing diastolic blood pressure 71 ± 11 vs 74 ± 12, $P < 0.02$). Gastrointestinal problems were the most common adverse effects ($n = 39$, 19%) reported. The overall efficacy of pyridostigmine in our study was seen in 42% of total patients or 52% of patients who could tolerate taking the drug.*

Conclusion: *The subgroup of POTS patients who can tolerate oral pyridostigmine may demonstrate improvement in their standing HR, standing diastolic blood pressure, and clinical symptoms of orthostatic intolerance. (PACE 2011; 1–6)*

pyridostigmine, orthostatic intolerance, postural orthostatic tachycardia syndrome

Introduction

Postural orthostatic tachycardia syndrome (POTS) is a form of chronic orthostatic intolerance associated with an excessive increase in heart rate (HR) during upright posture that resolves with recumbency. While the exact incidence is unknown, it is currently thought that POTS affects more than 500,000 people in the United States alone. POTS patients can suffer from variety of symptoms such as palpitations, exercise intolerance, lightheadedness, cognitive impairment, and syncope.[1] Many POTS patients can be severely limited in daily activities to the point of functional disability with loss of both educational and employment opportunities. A number of therapeutic options have been proposed for these patients, including increased hydration and sodium intake, reconditioning and strength training, as well as pharmacotherapy such as fludrocortisone, midodrine, serotonin and/or norepinephrine reuptake inhibitors, and octreotide. However, there are patients where these treatments are ineffective and/or poorly tolerated.[2]

Pyridostigmine, an acetyl cholinesterase inhibitor, is a novel treatment option for the patients suffering from POTS, presumably acting through facilitation of ganglionic and neural transmission in both the sympathetic and parasympathetic

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nerves.[3] A study by Raj et al. demonstrated that pyridostigmine improved both the tachycardia and other symptoms in a group of 17 patients suffering from POTS.[4] In this paper, we report our experience using pyridostigmine in a clinical setting with a large outpatient group of POTS patients refractory to other forms of treatment.

Methods

The study was a retrospective study approved by our institutional review board. We screened 300 POTS patients who were being followed at our institution's Syncope and Autonomic Disorders Center. A total of 208 patients were found eligible for inclusion in the current study.

Criterion for Diagnosis of POTS

POTS was defined as the presence of chronic symptoms of orthostatic intolerance (>6 months duration) accompanied by a reproducible HR increase of at least 30 beats/min (or a rate that exceeded 120 beats/min) that occurs in the first 10 minutes of upright posture or head-up tilt test (HUTT) occurring in the absence of other chronic debilitating disorders. Symptoms include fatigue, orthostatic palpitations, exercise intolerance, lightheadedness, diminished concentration, headache, near syncope, and syncope.[5] In a retrospective detailed chart review, we collected data including demographic information, presenting symptoms, laboratory data, tilt-table response, and treatment outcomes.

HUTT Protocol

The protocol used for tilt-table testing has been described elsewhere, but basically consisted of a 70° baseline upright tilt for a period of 30 minutes, during which time HR and blood pressure were monitored continually. If no symptoms occurred, the patient was lowered to the supine position and an intravenous infusion of isoproterenol started with a dose sufficient to raise the HR to 20%–25% above the resting value. Upright tilt was then repeated for a period of 15 minutes. Patients were included in the study if they had a POTS pattern on HUTT (rise in HR independent of any change in blood pressure).

Treatment Protocols

The treatment protocols that were initially employed were based on our previous experiences with orthostatic disorders and are described in detail elsewhere. We identified 208 patients with POTS who were refractory to other commonly used medications. Briefly, a sequence of therapies were employed that included physical counter maneuvers and aerobic and resistance training as well as increased dietary fluids and sodium. If these were ineffective, pharmacotherapy was initiated in a sequence generally consisting of fludrocortisone, midodrine, and selective serotonin reuptake inhibitors, either alone or in combination. A trial of stimulants including methylphenidate or dextroamphetamine failed to provide symptomatic relief in any of these patients. Being a referral center for POTS patients, our study had a higher number of drug refractory patients. As such, these refractory POTS patients were on multiple medications upon presentation and pyridostigmine was added in slow escalating doses to assess response and efficacy of pyridostigmine in this group of patients. The idea was to assess the use of the drug as it would be employed by a clinician in a "real world" setting as an "add on" to existing therapy. We did not employ a formal questionnaire or a composite autonomic severity score (CASS) to assess the response to treatment, nor did we assess the response to treatment with HUTT testing. The information about the current symptoms, side effects of medications, and overall improvement in symptoms from each patient were collected from the patient charts, physician communications, and direct patient inquiry. We also attempted to collect information about the prior trials of various medications before initiation of the pyridostigmine; however, that information was not available in the majority of the patients. A treatment was considered successful if the patient reported symptomatic relief and if the hemodynamic parameters showed improvement as compared to previous readings. HR and blood pressure were recorded both in supine and after 3 minutes of standing during each visit. We used descriptive statistics to report our findings.

Follow-up

The mean duration of follow-up was 12 ± 3 (range 9–15 and median 12) months.

Pyridostigmine Use

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. Again after a 1- to 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 180 mg of the sustained release form.

Results

We screened 300 patients diagnosed with POTS from our Syncope and Autonomic Dysfunction Clinic and found 208 patients eligible for inclusion in the current analysis (Fig. 1). Table I

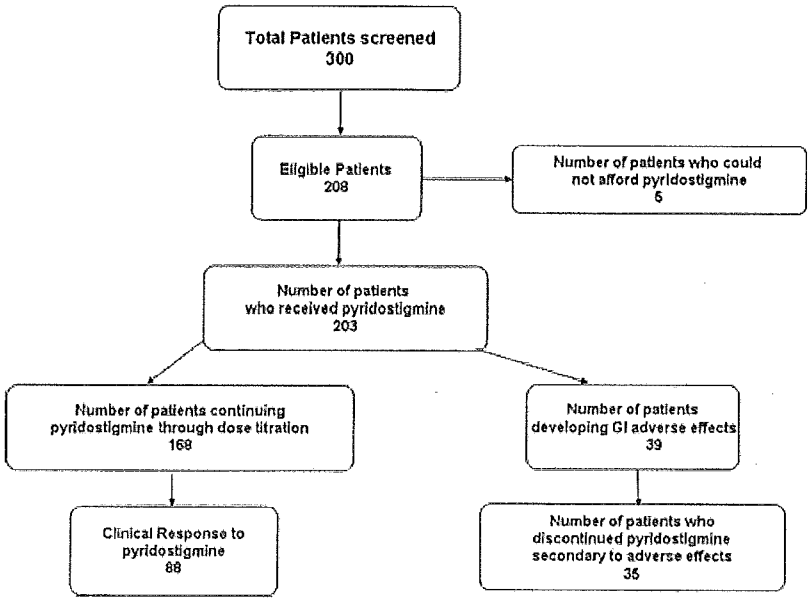

Figure 1. *Diagram summarizing the design and response to pyridostigmine in patients suffering from refractory POTS.*

shows the baseline clinical characteristics of the study group.

Two hundred eight patients (183 [88%] of whom were women) were found eligible for this study. Of the 208 patients who were found to be candidates for pyridostigmine only 203 received the medicine. Five patients could not afford the medication and were excluded from the analysis. Thirty five (17%) patients stopped the medication as a result of a variety of reported side effects. A total of 172 patients were able to tolerate the medication through its dose titration and were included in final analysis. The majority of our patients (80%) received 60 mg of pyridostigmine three times a day.

Effect of Pyridostigmine on Clinical Symptoms

Pyridostigmine improved symptoms of orthostatic intolerance in 88 of 203 (43%) of total patients or 88 of 172 (51%) who were able to tolerate the drug. The symptoms that improved most included fatigue (55%), palpitations (60%), presyncope (60%), and syncope (48%).

Effect of Pyridostigmine on Hemodynamic Parameters

Table II demonstrates effects of pyridostigmine on HR and blood pressure before and after treatment. Pyridostigmine significantly improved standing HR and standing diastolic blood pressure; however, there was no significant increase in standing systolic blood pressure.

Side Effects from Pyridostigmine

A total of 39 patients developed gastrointestinal (GI) symptoms; however, these symptoms were considered severe enough to warrant discontinuation of the therapy in 35 patients. These adverse effects included severe abdominal cramps, severe nausea, and diarrhea. Four patients had very mild bloating and mild nausea and they continued with the therapy. None of the patients had diarrhea to begin with and none had any previous history of diarrhea-predominant irritable bowel syndrome. Other minor side effects included neuromuscular (tremors, twitching, hyperhidrosis) in five (2.4%), urinary urgency in two (1%), hypertension in two (1%), chest pain in one (0.5%), and hypotension in one (0.5%).

We did not identify any clinical predictors that would portend a favorable response to pyridostigmine therapy. In our study, there did not appear to be relationship between dosage and the incidence of side effects.

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 an enhanced neural transmission, which improves baroreceptor reflex functions.[3] This augmented baroreceptor sensitivity that occurs with pyridostigmine has

Table I.

Baseline Clinical Characteristics of Patients

Study Characteristics	
Total number of patients screened	300
Number of patients who met inclusion criterion	208
Number of patients who received mestinon	203 (97.6%)
Total number of patients who developed intolerance to pyridostigmine.	35 (17%)
Number of patients with incomplete follow-up	33 (16%)
Type of POTS	
Neuropathic	171 (82%)
Hyperadrenergic	27 (18%)
Clinical features in patients included for analysis	
Age (years)	26 ± 12
Females (N %)	183 (88%)
Comorbidities (N, %)	
Joint hyper mobility	57 (27.4%)
Hypertension	30 (14%)
Diabetes mellitus	12 (5.8%)
Migraine	88 (42%)
Precipitating event	
Viral infection	35 (16.8%)
Pregnancy	4 (1.9%)
Surgery	5 (2.4%)
Trauma	7 (3.4%)
Lightning	1 (0.5%)
Clinical symptoms of POTS	
Fatigue	196 (94%)
Dizziness	196 (94%)
Presyncope	206 (99%)
Syncope	117 (56.3%)
Inability to concentrate	191 (92%)
Orthostatic palpitations	200 (96%)
Chest pain	82 (39%)
Hypersomnolence	119 (57%)
Response to pyridostigmine	
Number of patients reporting response	88 (42.3%)
Concomitant medications	
Methylphenidate	30 (14.7%)
β-blockers	108 (53%)
Scopolamine	17 (8.3%)
Norepinephrine reuptake inhibitors/selective serotonin reuptake inhibitors	84 (41.3%)
Midodrine	86 (42.3%)
Modafinil	31 (15.3%)
Fludrocortisone	65 (32%)
Octreotide	10 (4.9%)
Erythropoietin	13 (6.4%)

Table II.

Hemodynamic Effects of Pyridostigmine

	Before Treatment	After Treatment	P Value
Sitting heart rate	77 ± 14	76 ± 13	NS
Standing heart rate	94 ± 19	82 ± 16	0.003
Sitting systolic blood pressure	111 ± 17	115 ± 16	NS
Standing systolic blood pressure	106 ± 19	109 ± 19	NS
Sitting diastolic blood pressure	75 ± 11	75 ± 13	NS
Standing diastolic blood pressure	71 ± 11	74 ± 12	0.02

been shown to have a beneficial role in patients suffering from neurogenic orthostatic hypotension (NOH).[6] 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.[7] Further, improvement in patient satisfaction using CASS questionnaire has also been seen following chronic pyridostigmine therapy. In an open-label study, 20 of 28 patients with NOH receiving pyridostigmine reported marked improvement using CASS questionnaire at 19 ± 8.9 months of follow-up.[8] While there are some data to support the use of pyridostigmine in NOH, the role of pyridostigmine in POTS is limited to a single study. In this study by Raj et al.,[4] 17 patients with POTS were randomized to treatment with pyridostigmine (30 mg) and placebo. Baseline blood pressure and HR were recorded and compared with change in blood pressure and HR at 2 and 4 hours. Pyridostigmine use was associated with significant decrease in standing HR at 2 hours (119 ± 16 beats per minute [bpm] at baseline vs 2 hours, 104 ± 16 bpm, $P < 0.001$) and continued at 4 hours (100 ± 16 bpm, $P < 0.001$). The authors proposed that acute pyridostigmine therapy induced a shift in cardiovagal tone that was associated with reduction in upright tachycardia in POTS patients. Similar effects on parasympathetic tone have been reported in heart failure in patients receiving pyridoigmine therapy.[9]

Despite this, the data on the long-term clinical efficacy of pyridostigmine in POTS patients in a clinical setting has yet to be determined. POTS is a chronic autonomic disorder, displaying wide fluctuations in both hemodynamics as well as patient symptoms due to factors such as environmental conditions, disease progression,

resistance to therapy, and other concurrent illness. In the current analysis, pyridostigmine use was associated with improvement in the clinical symptoms of POTS, with the symptoms of fatigue, palpitations, presyncope, and syncope showing the greatest response. The improvement in these symptoms was most likely related to improved hemodynamics observed following pyridoigmine administration. In addition, the use of pyridostigmine was associated with a significant and sustained improvement in orthostatic tachycardia in our study population. This is comparable to the findings reported by Raj et al.[4] Besides improvement in cardiovagal tone, sustained improvement in upright tachycardia as seen in our study also suggests the absence of a rapid tachyplaxis with long-term therapy. We did not identify any clinical characteristics that would predict a favorable response to pyridostigmine therapy. This limitation in the current analysis would require a large prospective randomized study in the future to help identify the subgroup of POTS patients who may most benefit from pyridostigmine therapy.

Pyridostigime has been postulated to improve sympathetic vasomotor tone and has favorable effect on hemodynamics in several forms of autonomic dysfunction. Singer et al. in a double-blinded, placebo-controlled cross over study in 58 patients with neurogenic hypotension, showed that the use of pyridostigmine with midodrine was associated with improvement in standing diastolic blood pressure without any supine hypertension.[7] In our study, we also observed significant improvement in standing diastolic blood pressure in POTS patients. This increase in diastolic blood pressure suggests an increase in peripheral vascular resistance following pyridostigmine administration. Similar to previous studies we did not note any significant effects on upright systolic blood pressure. Further, we did not observe any increase in supine hypertension on pyridostigmine therapy.

The overall efficacy of pyridostigmine in our study was seen in 42% of total patients or 51% of patients who could tolerate taking the drug. However, we did not find any specific characteristic feature that could predict a response to pyridostigmine therapy. The possible reasons for lack of improvement were noncompliance, possible progression of the disease, resistant forms of POTS, and intolerance due to side effects of therapy. In our patient population, GI distress was the most common side effect followed by neuromuscular and genitourinary problems, similar to that reported in previous studies. The GI symptoms were severe enough in 35 (17%) and pyridostigmine therapy was subsequently discontinued in this subgroup of patients. Pyridostigmine was used as an add-on therapy for the treatment of POTS; however, there was no clear drug-drug interaction observed in our study group.

Limitations

There are certain important limitations in the design of the current study. The study group itself was small, and it was not a randomized controlled trial. Rather, each patient was used as his/her own control. Also, our study lacked a standardized criterion for evaluating efficacy of therapy. In addition, the assessment of hemodynamic responses was also not standardized. The beneficial effects noted in our study could represent a spontaneous remission in some of these patients. However, the refractory nature of the symptoms in this group of patients would seem to argue against chance improvement. Our patients were highly symptomatic and had not responded to multiple therapeutic trials of various medications. All patients presented here were suffering from unusually severe and refractory forms of POTS and therefore may not represent the majority of patients with POTS. We hope this study will lay a foundation for a larger randomized clinical trial that will effectively evaluate the role of pyridostigmine in the treatment of POTS. Also, such a study will help to identify those POTS patients who are likely to benefit from pyridostigmine.

Pyridostigmine therapy may help ameliorate the refractory symptoms in patients suffering from the severe forms of this disorder. Our study did not evaluate the use of pyridostigmine as a first-line therapy in POTS, as it was added to existing therapies.

Conclusion

In a subgroup of POTS patients refractory to other forms of therapy, long-term treatment with pyridostigmine reduces standing HR, improves standing diastolic blood pressure, and ameliorates many clinical symptoms in patients who can tolerate taking this medication. The utility of the pyridostigmine as a first-line therapy in POTS remains unknown from the results of this limited study.

References

1. Grubb BP, Kanjwal Y, Kosinski DJ. The postural tachycardia syndrome: A concise guide to diagnosis and management. J Cardiovasc Electrophysiol 2006; 17:108–112.
2. Grubb BP, Kosinski DJ, Kanjwal Y. Orthostatic hypotension: Causes, classification, and treatment. Pacing Clin Electrophysiol 2003; 26:892–901.
3. Gales BJ, Gales MA. Pyridostigmine in the treatment of orthostatic intolerance. Ann Pharmacother 2007; 41:314–318.
4. Raj SR, Black BK, Biaggioni I, Harris PA, Robertson D. Acetylcholinesteras inhibition improves tachycardia in postural tachycardia syndrome. Circulation 2005; 111:2734–2740.
5. Kanjwal Y, Kosinski D, Grubb BP. The postural orthostatic tachycardia syndrome: Definitions, diagnosis, and management. Pacing Clin Electrophysiol 2003; 26:1747–1757.
6. Argiles Monge JA, Leiva Santana C. Pyridostigmine in the treatment of primary orthostatic hypotension. Neurologia 2007; 22:260–262.
7. Singer W, Opfer-Gehrking TL, Nickander KK, Hines SM, Low PA. Pyridostigmine treatment trial in neurogenic orthostatic hypotension. Arch Neurol 2006; 63:513–518.
8. Sandroni P, Opfer-Gehrking TL, Suarez GA, Klein CM, Hines S, O'Brien PC, Slezak J, et al. Pyridostigmine for treatment of neurogenic orthostatic hypotension [correction of hypertension]–a follow-up survey study. Clin Auton Res 2005; 15:51–53.
9. Behling A, Moraes RS, Rohde LE, Ferlin EL, Nórega AC, Ribeiro JP. Cholinergic stimulation with pyridostigmine reduces ventricular arrhythmia and enhances heart rate variability in heart failure. Am Heart J 2003; 146:494–500.