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Use of Octreotide in the Treatment of Refractory Orthostatic Intolerance

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There have been reports on the use of octreotide in patients with orthostatic hypotension, postural tachycardia syndrome, and orthostatic syncope. However, there are little if any data on the use of octreotide in patients who have failed multiple other medications. This study was a retrospective chart analysis and was approved by our Institutional Review Board. A total of 12 patients were identified for inclusion in this study. The diagnosis of orthostatic intolerance was based on patient history, physical examination, and response to Head Up Tilt Table testing. These patients had failed multiple medications and were ultimately treated with octreotide. In a retrospective chart review, we collected data, including demographic information, presenting symptoms, laboratory data, tilt-table response, standing heart rate, standing blood pressure before and after treatment (wherever available), and treatment outcomes. Twelve patients aged 33 ± 18 years, eight (66.7%) females, were found to have symptoms of refractory orthostatic intolerance and failed multiple regimens of medication and were ultimately treated with octreotide administration. Five patients (41.7%) had demonstrated a postural tachycardia syndrome pattern, five (41.7%) a neurocardiogenic, and two (16.6%) a dysautonomic response on a Head Up Tilt Table. Symptoms of syncope and orthostatic palpitations improved in six (50%) of the patients. Standing heart rate was significantly reduced after octreotide administration (80 ± 8 versus 108 ± 13; $P < 0.05$). The standing systolic blood pressure was increased after octreotide administration (107 ± 26 versus 116 ± 22). Three patients (25%) reported complete elimination of syncope, whereas another three had reduction in the frequency of their syncope. However, symptoms of fatigue improved only in two (29%) of the seven patients. Octreotide may improve symptoms in some patients with refractory orthostatic intolerance.

Keywords: orthostatic intolerance, postural tachycardia syndrome, octreotide

INTRODUCTION

There have been reports on the use of octreotide in patients with orthostatic hypotension,[1,2] postural tachycardia syndrome, and orthostatic syncope.[3,4] Orthostatic intolerance (OI) refers to a heterogeneous group of disorders of hemodynamic regulation characterized by insufficient cerebral perfusion resulting in symptoms on standing and relieved by becoming supine.[5–9] Symptoms may include syncope, near syncope, lightheadedness, exercise intolerance, palpations, cognitive impairment, headache, and fatigue.[5–9] Many of these patients may be refractory to the commonly used medications and the management of these patients can sometimes be quite challenging as well as frustrating for both the patient and the treating physician. We report on the use of octreotide in the treatment of patients with OI who failed multiple medication aimed at reliving their symptoms of OI.

METHODS

The study was a retrospective chart analysis and was approved by our Institutional Review Board. A total of 12 patients were identified for inclusion in this study.

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The diagnosis of OI was based on patient history, physical examination, and response to Head Up Tilt Table (HUTT) testing.

These patients had failed multiple medications and were ultimately tried with octreotide. In a retrospective chart review, we collected data, including demographic information, presenting symptoms, laboratory data, tilt-table response, standing heart rate, standing blood pressure before and after treatment (wherever available), and treatment outcomes.

Head up tilt test protocol

The protocol used for tilt-table testing has been described elsewhere,[5–9] but basically consisted of a 70° baseline upright tilt for a period of 30 minutes, during which time heart rate and blood pressure were monitored continually. If symptomatic hypotension and bradycardia occurred, reproducing the patient's symptoms, the test was ended. 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 heart rate to 20% to 25% above the resting value. Upright tilt was then repeated for a period of 15 minutes. These data were categorized into three groups based on the positive tilt-table pattern: neurocardiogenic, dysautonomic, and postural orthostatic tachycardia syndrome.

Treatment protocols

The treatment protocols used were based on our previous experiences with orthostatic disorders and are described in detail elsewhere.[1–5] We identified 12 patients with OI with symptoms refractory to other commonly used medication and had failed multiple medications either singly or in combination. Briefly, a sequence of therapies was used that included physical counter maneuvers as well as increased dietary fluids and sodium. If these were ineffective, pharmacotherapy was initiated in a sequence generally consisting of fludrocortisone, midodrine, methylphenidate, selective serotonin reuptake inhibitors, pyridostigmine, and erythropoietin either alone or in combination. All of these patients were subsequently started on octreotide. Octreotide was administered by subcutaneous injection beginning at 50 μg two to three times daily and titrating to the maximum dose of 100 μg three times daily.

Response to treatment

We collected the information about the symptoms of OI before and after initiating octreotide. The heart rate and blood pressure responses before and 2 months after being on octreotide were collected. We did not use a formal questionnaire for assessing the response to therapy; however, response to therapy was considered successful if it provided symptom relief. The response to octreotide was not assessed by a repeat HUTT.

Statistics

The data are presented either as means ± standard deviation or percent changes. *T* test was used to compare means and the statistical significance was reached at the *P* value of < 0.05. All statistical analysis was done using SPSS 16 (SPSS Inc, Chicago, IL).

RESULTS

Twelve patients aged 33 ± 18 years, eight (66.7%) females, were found to have symptoms of refractory OI, who failed multiple regimens of medication and were ultimately treated with octreotide. Table 1 summarizes the baseline clinical features of our study population.

Response to head up tilt table

Five patients (41.7%) had demonstrated a postural orthostatic tachycardia syndrome pattern, five (41.7%)

Table 1. Baseline clinical characteristics of the study patients (n = 12).

Age	33 ± 18
Sex (females)	8 (66.7%)
Type of orthostatic intolerance	
Postural tachycardia syndrome	5 (41.7%)
Neurocardiogenic syncope	5 (41.7%)
Dysautonomia	2 (16.6)
Symptoms of orthostatic intolerance	
Orthostatic palpitations	12 (100%)
Dizziness	9 (75%)
Inability to concentrate	12 (100%)
Syncope	12 (100%)
Fatigue	7 (58.3%)
Medications	
Beta-blockers	5 (41.7%)
SSRI	4 (33%)
Norepinephrine re-uptake inhibitor/SSRI	7 (58.3%)
Midodrine	8 (66.7%)
Modafinil	6 (50%)
Fludrocortisone	
Comorbid conditions	
Hypermobility	4 (33.3)
Hypertension	4 (33.3)
Diabetes mellitus	3 (25%)
Migraine	5 (41.7%)
Precipitating factor	
None	10 (83.3%)
Infectious mononucleosis	2 (16.6%)
Adverse events	
Dizziness	1 (8.3%)
Diarrhea	1 (8.3%)

SSRI, selective serotonin reuptake inhibitor.

Table 2. Heart rate and blood pressure responses before and after octreotide administration.

	Before octreotide treatment	After octreotide treatment	*P*
Standing heart rate	108 ± 13	80 ± 8	0.004
Standing systolic blood pressure	107 ± 26	116 ± 22	0.02
Standing diastolic blood pressure	72 ± 18	75 ± 17	0.2

a neurocardiogenic, and two (16.6%) a dysautonomic response on a HUTT. All patients had reproduced their symptoms while on HUTT, which were similar to their spontaneous clinical symptoms.

Symptoms of orthostatic intolerance

Syncope, near syncope, and orthostatic palpitations were reported by all patients. Dizziness and fatigue were reported by nine (75%) and seven (53%) each, respectively.

Comorbidity

Migraine was the most common comorbidity seen in five (41%) followed by joint hypermobility and hypertension seen in four (33.3%) patients each. Diabetes was reported by three (25%) patients.

Activities of daily living

Symptoms of OI had resulted in a significant impairment in the activities of daily living in each patient. Each of the patients reported a constant fear of experiencing syncope. This fear had greatly limited their daily activities to a point that they were scared of even assuming an upright posture and had become

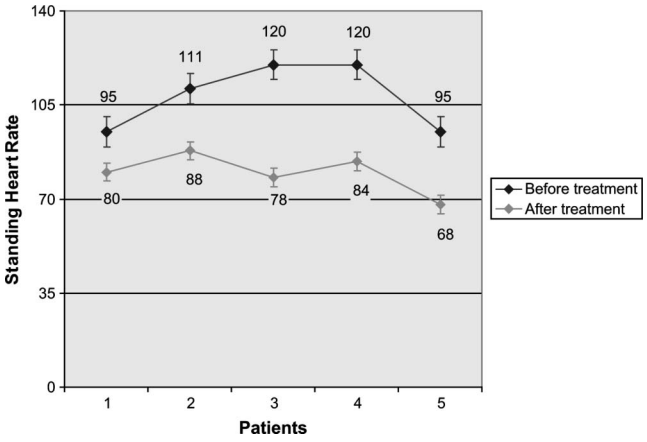

FIGURE 1. Effect of octreotide on standing heart rate of patients with postural tachycardia syndrome.

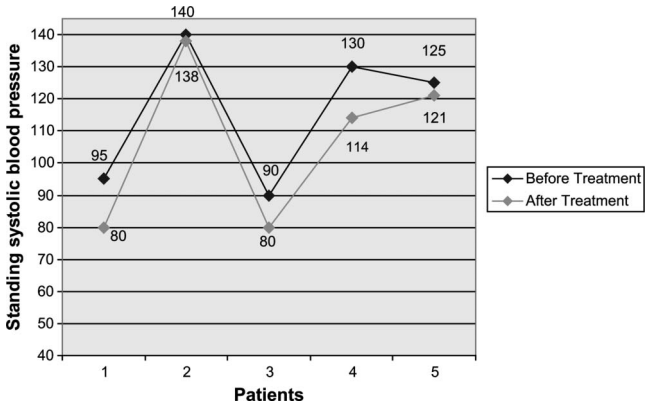

FIGURE 2. Effect of octreotide on standing systolic blood pressure in patients with postural tachycardia syndrome.

home-bound. Loss of jobs or inability to engage in school activities was reported by each patient.

Heart rate and blood pressure responses to octreotide administration

Of 12 patients, information about standing heart rate and blood pressure before and after octreotide administration was available in only five patients (Table 2; Figs. 1–3). Standing heart rate was significantly reduced after octreotide administration (80 ± 8 versus 108 ± 13; $P < 0.05$; Fig. 1). The standing systolic blood pressure was increased after octreotide administration (107 ± 26 versus 116 ± 22; $P < 0.05$; Fig. 2). An increase in diastolic blood pressure was not statistically significant (Fig. 3).

Activities of daily living and symptoms of orthostatic intolerance after octreotide administration

Symptoms of syncope and orthostatic palpitations improved in six (50%) of the patients. Three patients (25%) reported complete elimination of syncope, whereas another three had reduction in the frequency

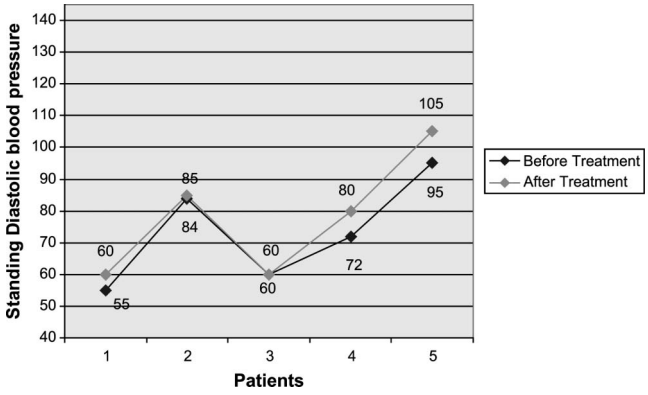

FIGURE 3. Effect of octreotide on standing diastolic blood pressure in patients with postural tachycardia syndrome.

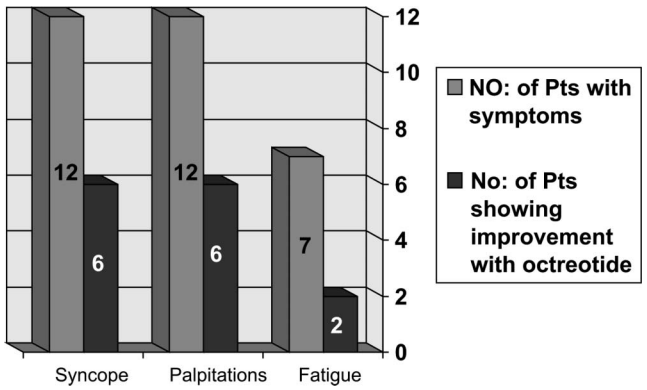

FIGURE 4. Effect of octreotide use on symptoms of patients with orthostatic intolerance.

and severity of their syncope. However, symptoms of fatigue improved only in two (29%) of the seven patients (Fig. 4). These five patients continued to have debilitating fatigue while subsequently treated with modafinil. Also, six (50%) patients reported subjective improvement in their activities of daily living and were able to resume their employment or colleges.

DISCUSSION

Octreotide is a somatostain analog that is known to increase blood pressure in patients with orthostatic hypotension.[1,2,10] There are reports on the use of octreotide in patients with OI.[3,4] However, there are little if any data on the use of octreotide in patients who fail multiple medications.

In this study, octreotide was used in 12 patients who had failed multiple medications either alone or in combination. Octreotide demonstrated a favorable hemodynamic effect by improving heart rate response to standing as well as by improving systolic blood pressure. The improvements in symptoms of OI, although modest, are encouraging in this small-sized patient group. One of the reasons for the modest response observed in our patients would be attributed to the small size and the fact that the patients were refractory to other therapies as well and were not randomly allocated to the treatment; also, there was no control group. These patients served as their own control subjects. In addition, patients with OI may exhibit spontaneous variations in symptom severity. Hence, we cannot be absolutely sure that the beneficial effects noted can be wholly attributed to the actions of the drug. However, this group of patients had severe refractory OI and had not responded to any other therapeutic modality. Thus, it seems reasonable to conclude that octreotide contributed to the beneficial effects noted. Finally, the patients presented here all tended to have unusually severe forms of the disorder and therefore may not be representative of the majority of patients with OI. Until more results from randomized controlled trials become available, use of octreotide should be limited to patients with refractory symptoms of OI.

CONCLUSION

Octreotide may improve symptoms in some patients with refractory OI.

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