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# Use of Methylphenidate in the Treatment of Patients Suffering From Refractory Postural Tachycardia Syndrome

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Methylphenidate has been shown to be an effective therapy in patients with refractory neurocardiogenic syncope. However, the role of methylphenidate in patients suffering from postural orthostatic tachycardia (POTS) has not been reported. The study was approved by the institutional review board. A retrospective nonrandomized analysis was performed on 24 patients evaluated at our autonomic center for POTS from 2003 to 2010. The diagnosis of POTS was based on patient history, physical examination, and response to head up tilt table testing. The mean follow-up period was  $9 \pm 3$  months. The patients were included in the current study if they had a diagnosis of POTS with severe symptoms of orthostatic intolerance and were refractory to the commonly used medications. All of these patients were started on methylphenidate and the response to therapy was considered successful if it provided symptomatic relief. Twenty-four patients (age  $28 \pm 12$ , 20 women) met inclusion criterion for this study. The response to treatment was assessed subjectively in each patient and was collected in a retrospective fashion from patient charts and physician communications. Four patients reported side effects in the form of nausea and 2 ultimately had to discontinue the treatment. Another 4 patients had a follow-up of less than 6 months. Thus, only 18 patients who received methylphenidate completed the follow-up of 6 months. Out of these 18 patients, 14 (77%) patients reported marked improvement in their symptoms. Nine out of 12 patients who had recurrent episodes of syncope reported no syncope at 6 months of follow-up. Fourteen (77%) patients reported marked improvement in their symptoms of fatigue and presyncope. Four patients continue to have symptoms of orthostatic intolerance and 3 continued to have recurrent episodes of syncope. Methylphenidate may be beneficial in patients with otherwise refractory postural tachycardia syndrome.

*Keywords:* methylphenidate, ritalin, postural tachycardia syndrome

## INTRODUCTION

Postural orthostatic tachycardia (POTS) is a condition causing symptoms of orthostatic intolerance (of greater

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than 6 months duration) accompanied by a heart rate increase of at least 30 beats/min (or a rate that exceeds 120 beats/min) that occurs in the first 10 minutes of upright posture or head up tilt occurring in the absence of other chronic debilitating disorders.<sup>1–4</sup> It occurs principally due to failure of the peripheral vasculature to maintain adequate resistance during orthostatic stress, permitting excessive venous pooling to occur. The resultant increase in heart rate and myocardial contractility attempts to compensate for the reduced circulating blood volume. There are roughly 500,000 to 1,000,000 people suffering from POTS in United States.<sup>5,6</sup> Multiple pharmacotherapeutic agents including fludrocortisone, midodrine, bupropion, selective

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serotonin reuptake inhibitors have been used to prevent symptoms of orthostatic intolerance in these patients. However, there are some patients who are refractory to these pharmaceutical agents. Methylphenidate has been reported to help symptoms of orthostatic intolerance in patients with refractory neurocardiogenic syncope.<sup>7</sup> Methylphenidate (Ritalin), a piperidine derivative that is structurally related to amphetamine, has a hemodynamic profile similar to amphetamine, but with a much lower incidence of side effects and much favorable safety profile.<sup>8–10</sup> The aim of this study was to determine whether methylphenidate can be helpful in patients with POTS refractory to other medication.

## METHODS

A retrospective nonrandomized analysis was performed on 24 patients evaluated at our autonomic center for POTS from 2003 to 2010. The study was approved by the institutional review board.

### Criterion for diagnosis of POTS

POTS is defined as symptoms of orthostatic intolerance (of greater than 6 months duration) accompanied by a heart rate increase of at least 30 beats/min (or a rate that exceeds 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. In a retrospective 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-degree baseline upright tilt for a period of 30 minutes, during which time heart rate 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 heart rate 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 heart rate without any change in blood pressure). The treatment protocols employed were based on our previous experiences with orthostatic disorders and are described in detail elsewhere.<sup>2–4,11–15</sup> We identified 24 patients of POTS who were refractory to other

commonly used medications. Briefly, a sequence of therapies was employed that included physical counter maneuvers and aerobic and resistance training and increased dietary fluids and sodium. If these were ineffective, pharmacotherapy was initiated in a sequence generally consisting of fludrocortisone, midodrine, selective serotonin reuptake inhibitors, either alone or in combination. A trial of stimulants including amphetamine or dextroamphetamine failed to provide symptomatic relief in these patients. The patients were included in the current study if they had a diagnosis of POTS (described earlier) and were having symptoms of orthostatic intolerance and were refractory to the commonly used medications. All of these patients were subsequently tried on methylphenidate. We did not employ a formal questionnaire to assess the response to treatment nor did we assess the response to treatment with HUTT testing. The information about the subjective symptoms and sense of well being from each patient were collected from the patient charts, physician communications, and direct patient inquiry. A treatment was considered successful if it provided symptomatic relief.

## RESULTS

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We screened 100 patients who followed our syncope and autonomic center clinic. We found 24 patients (age  $28 \pm 12$ , 20 women) who met inclusion criterion for this study. Table 1 summarizes the clinical characteristics of the study population. TI

### Methylphenidate administration

Each patient had received methylphenidate 10-mg po 3 times per day 15–30 minutes before meals, and the effects were evaluated every month for a mean of  $9 \pm 3$  months.

### Clinical profile of POTS patients

Twenty-three patients had the partial dysautonomic form of POTS and 1 patient had hyperadrenergic form of POTS. The common precipitating factor noted in this group was viral infection and the common comorbidities noted were migraine in 10 (41%) and joint hypermobility in 7 (29%) of patients. The most common symptom in this group of patients was presyncope 21 (87%), orthostatic palpitations 21 (87%), and fatigue 17 (70%). Syncope was reported by 12 (50%) and inability to concentrate by 10 (59%) patients.

### Response to treatment

The response to treatment was assessed subjectively in each patient and was collected in a retrospective

**Table 1.** Clinical characteristics of patients suffering from drug refractory postural tachycardia syndrome.

Study characteristics	
Total number of patients screened	100
Number of patients who met inclusion criterion	24
Total number of patients who developed intolerance	4 (17%)
Number of patients who discontinued Methylphenidate (due to intolerance)	2 (8.5%)
Number of patients with incomplete follow-up	4 (16%)
Type of POTS	
Partial dysautonomic	23 (95%)
Hyperadrenergic	1 (5%)
Clinical features in patients included for analysis	
Age (yrs)	28 ± 12
Females (N, %)	20 (83%)
Comorbidities (N, %)	
Joint hypermobility	7 (29%)
Hypertension	3 (13%)
Diabetes mellitus	3 (13%)
Migraine	10 (41%)
Precipitating event	
Viral infection	49 (17%)
Pregnancy	1 (4.2%)
Surgery	1 (4.2%)
Trauma	1 (4.2%)
Clinical symptoms of POTS	
Fatigue	17 (70%)
Presyncope	21 (87%)
Syncope	12 (50%)
Inability to concentrate	10 (41%)
Orthostatic palpitations	21 (87%)
Response to methylphenidate	
Number of patients reporting response to methylphenidate	14 (59%)

fashion from patient charts and physician communications and patient inquiry. A total of 24 patients were evaluated. Four patients reported side effects in the form of nausea and 2 ultimately had to discontinue the treatment. Another 4 patients had a follow-up of less than 6 months. Thus, only 18 patients who received methylphenidate completed the follow-up of 6 months. Out of these 18 patients, 14 (77%) patients reported a marked improvement in their symptoms. Nine out of 12 patients who had previously experienced recurrent episodes of syncope reported no syncope at 6 months of follow-up. Fourteen (77%) patients reported marked improvement in their symptoms of fatigue and presyncope. Four patients continued to have symptoms of orthostatic intolerance and 3 continued to have recurrent episodes of syncope (Table 1).

## DISCUSSION

Because one of the cardinal features of the POTS is a failure to maintain vascular resistance during orthostatic stress, many therapies are aimed at increasing vascular tone.<sup>1-5</sup> Midodrine hydrochloride is an example of a peripheral alpha-1 receptor stimulant that is marketed for the treatment of orthostatic disorders.<sup>16-20</sup> Although effective in some patients, its use is limited by patient complaints of nausea and sensation of "goose bumps" and scalp tingling.<sup>16-20</sup> The search for an effective alternative agent for patients in whom midodrine was either ineffective or not tolerated led us to explore the use of chemically similar ephedra alkaloid agent methylphenidate.

Methylphenidate (Ritalin) is a piperidine derivative that is structurally similar to amphetamine.<sup>9</sup> It appears to act by releasing stored catecholamine from the reserpine sensitive presynaptic vesicular pool, decreasing their reuptake, inhibiting monamine oxidase, and has a direct postsynaptic alpha receptor stimulating action as well similar to that seen from midodrine.<sup>10</sup> Like amphetamine, methylphenidate is poorly bound to plasma proteins. It undergoes relatively rapid metabolism to an inactive metabolite, ritalinic acid. Although its peripheral vascular effects are quite similar to amphetamine, the side-effect profile of methylphenidate is felt to be significantly less, and its addictive potential is also considered much less.<sup>11</sup> This difference in side-effect profile has led it to become the treatment of choice in children with ADD.<sup>10,11</sup>

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Dextroamphetamine has been reported to be beneficial in the treatment of vasodepressor syncope. Susmano et al<sup>21</sup> reported use of dextroamphetamine for the prevention of vasodepressor syncope in 3 patients with vasodepressor syncope. A repeat HUTT after administration of dextro-amphetamine failed to reproduce hypotension or symptoms of syncope or presyncope in these 3 patients. Grubb et al reported on the use of methylphenidate in patients with refractory neurocardiogenic syncope.<sup>8</sup> In this report, 7 patients (all women mean age 31 ± 15 years) with recurrent syncope and positive head upright tilt induced hypotension/bradycardia (refractory to normal therapy) were placed on methylphenidate 10 mg orally 3 times per day. Six of the 7 patients became both tilt negative and clinically asymptomatic over a 7-month follow-up period. It was concluded that methylphenidate may be an effective therapy in patients with recurrent neurocardiogenic syncope refractory to other forms of therapy.<sup>8</sup>

In the current study, we found that methylphenidate may be potentially helpful in POTS patients in whom other therapies are ineffective, not tolerated or are

contraindicated. Initial therapies in the patients of POTS usually consist of an increase in salt and fluid intake and aerobic reconditioning with resistance training to increase lower extremity strength. Pharmacotherapy can be used alone or in combination in the following order: fludrocortisone 0.1 mg po bid, midodrine 5–10 mg po tid, propranolol 10 mg po tid, pyrodostigmine 60 mg po bid, serotonin reuptake inhibitor, modafinil 100 mg po qam, or dextroamphetamine. Not every patient receives every medication. Although majority of POTS patients will respond to the above mentioned therapies, however, there is a group of patients in whom these medications are either ineffective or poorly tolerated. In the current analysis, we found that methylphenidate can be effective in ameliorating symptoms of POTS in patients who failed other medications. There are also published reports that methylphenidate is safe when used for a long periods of time in the treatment of patients with orthostatic hypotension.<sup>22</sup> As was alluded to earlier, in patients with POTS, the main mechanism is the consistent failure of the peripheral vascular system to increase resistance during upright posture. A number of peripheral vascular constrictive agents have been used as therapeutic modalities in an attempt to augment peripheral vascular resistance in face of orthostatic stress.<sup>2–5,8,12–16</sup> Methylphenidate seems to be an effective vasoconstrictive agent with a reasonable safety profile that can be used as a chronic therapy for patients with symptomatic POTS. Although methylphenidate has a favorable safety profile it has a potential to exacerbate angina or cardiac arrhythmias. Other side effects may be anorexia, nausea, euphoria, dry mouth, and occasional anxiety.<sup>10</sup> In the current study, nausea was reported in 4 patients and it was severe enough to warrant discontinuation of this medication in 2 patients. Although the potential for addiction is considered to be much less than for amphetamines, very close supervision of the drug is required.<sup>11</sup> For these reasons, methylphenidate should be reserved only for otherwise refractory cases of POTS.

#### Limitation of activities of daily living

POTS in our study population has resulted in substantial limitation of daily activities. POTS can have tremendous effect on the quality of life often resulting in a severe limitation of daily activities. In addition, an often neglected but nonetheless important aspect of this disorder is the tremendous social, economical, and emotional toll it takes on the patients and their families. Although we did not employ a formal quality of life questionnaire, following treatment with methylphenidate 14 patients reported marked improvement in their activities of daily living.

#### Limitations

There are several important limitations to our study. The study group itself was small, and it was not a randomized-controlled trial. Rather, each patient was used as their own control. In addition, patients with POTS 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 was highly symptomatic who had not responded to any other therapeutic modality. Thus, it seems reasonable to conclude that methylphenidate 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 POTS.

#### CONCLUSIONS

Based on our observations in this study we conclude that methylphenidate may be a beneficial therapy in POTS patients who fail or are intolerant to first line therapy. A prospectively designed randomized study in future may better define the role this therapy in patients with POTS.

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