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Desmopressin acutely decreases tachycardia and improves symptoms in the Postural Tachycardia Syndrome (POTS)

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Abstract

Background—Postural Tachycardia Syndrome (POTS) induces disabling chronic orthostatic intolerance with an excessive increase in heart rate (HR) upon standing, and many POTS patients have low blood volume. Increasing blood volume is a promising approach to this problem.

Objective—We tested the hypothesis that desmopressin (DDAVP) will attenuate the tachycardia and improve symptom burden in patients with POTS.

Methods—In this protocol, patients with POTS (n=30) underwent acute drug trials with DDAVP 0.2 mg orally and placebo, on separate mornings, in a randomized crossover design. Blood pressure, HR and symptoms were assessed while seated and after standing for up to 10 minutes prior to and hourly for 4 hours following study drug.

Results—Standing HR was significantly lower following DDAVP compared to placebo (101.9 ± 14.5 vs. 109.2 ± 17.4 bpm (P<0.001)). Standing blood pressure was not affected (P=0.28). The symptom burden improved with DDAVP (from a score of 18 ± 18 to 13 ± 15 arbitrary units [au] at 2 hours) compared with placebo (from 18 ± 17 to 19 ± 16 au; P=0.010).

Conclusion—Oral desmopressin significantly attenuated tachycardia and improved symptoms in POTS. The safety profile of this approach would need to be examined before it can be recommended for routine treatment of these patients.

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Keywords

tachycardia; desmopressin; autonomic nervous system; blood volume; drugs; orthostatic intolerance

INTRODUCTION

Postural tachycardia syndrome (POTS) is a chronic disorder of the autonomic nervous system characterized by excessive increase in heart rate (HR) upon standing in the absence of orthostatic hypotension. POTS is estimated to affect 500,000 patients in the United States alone,[1] disproportionately affecting women of childbearing age.[2] Symptoms may include palpitations, lightheadedness, and mental clouding.[3] POTS is associated with significant functional deficits and diminished quality of life.[4,5]

There are several likely pathophysiologic mechanisms that may contribute to the symptoms of POTS. These include increased sympathetic tone,[2,6] partial autonomic neuropathy,[7] and low blood volume.[8,9] The treatment of low blood volume in POTS patients is still evolving and has scant data to support it. Acutely, the rapid infusion of normal saline can reverse the orthostatic tachycardia.[10] On a chronic basis, POTS patients are often advised to follow a high sodium diet (200–300 mEq/d) with significant water intake, though there are no data as to the effectiveness of this approach. Another treatment option is fludrocortisone, a mineralocorticoid agonist, to augment sodium retention and secondarily blood volume[11], but the increase in blood volume is transient.[12]

Desmopressin (DDAVP) is a synthetic version of arginine vasopressin, a natural antidiuretic hormone, and is commonly used to treat enuresis in children. DDAVP promotes fluid retention by increasing water permeability in the distal tubule of the kidney.[13] DDAVP elicits a greater antidiuretic response, but a reduced effect on smooth muscle contraction and vasopressor properties, when compared with vasopressin.[13] Finally, DDAVP, unlike vasopressin, does not stimulate ACTH release or increase plasma cortisol concentrations.[13] By enhancing fluid retention, DDAVP might promote acute blood volume expansion and reduce upright tachycardia. Therefore, we prospectively tested the hypothesis that DDAVP would decrease orthostatic tachycardia and improve symptoms in patients with POTS.

METHODS

Subjects

Patients referred to the Vanderbilt University Autonomic Dysfunction Center with POTS between November 2003 and September 2008 were candidates for inclusion in this study. Patients met criteria for POTS[3,14,15] in that they developed symptoms of orthostatic intolerance accompanied by a HR rise ≥30 bpm within 10 minutes of standing in the absence of orthostatic hypotension (a fall in blood pressure [BP] of >20/10 mmHg). All patients had at least a 6-month history of symptoms in the absence of an additional chronic disorder known to cause orthostatic intolerance and in the absence of prolonged bed rest. All patients were at least 18 years old. The Vanderbilt University Investigational Review Board approved this study. Written informed consent was obtained from each subject before initiating the study. The data reported are a part of "The Treatment of Orthostatic Intolerance" study, which is registered with http://www.clinicaltrials.gov (NCT00262470).

Study Diet and Baseline Characterization

Study investigations were performed in the Elliot V. Newman Clinical Research Center at Vanderbilt University. For at least 3 days before testing, subjects consumed a

methylxanthine-free diet containing 150 mEq/day of sodium and 70 mEq/day of potassium. Long-term medications were discontinued 5 half-life periods before the study. Fludrocortisone has an elimination half-life of 3.5 hours,[11] but this was discontinued for at least 5 days due to potential extended hormonal effects. HR, systolic BP (SBP), diastolic BP (DBP), mean arterial pressure (MAP) and fractionated plasma catecholamines were assessed after overnight rest with the patient in the supine position and again after standing up to 30 minutes (as tolerated) as part of baseline characterization. For catecholamine measurements, blood was collected in plastic syringes, immediately transferred to chilled vacuum tubes with sodium heparin (BD, Franklin Lakes, NJ), and placed on ice. Plasma was separated by centrifugation at −4°C and stored at −70°C in collection tubes with 6% reduced glutathione (Sigma-Aldrich Inc., St Louis, MO) until the assay was performed. Concentrations of norepinephrine and epinephrine were measured by batch alumina extraction followed by high-performance liquid chromatography for separation with electrochemical detection and quantification.[10] Plasma norepinephrine and epinephrine values are reported in SI units. To convert from nmol/L to the more conventional pg/mL, multiply by 169.18 for norepinephrine (1 nmol/L = 169.18 pg/mL) or by 183.2 for epinephrine (1 nmol/L = 183.2 pg/mL).

Medication Trials

These "proof of concept" drug trials were started in the morning at least 2 hours after an early, light breakfast (to avoid acute hemodynamic effects from eating) in a post-void state. In this trial, patients with POTS were given DDAVP 0.2 mg (Teva Pharmaceuticals, Israel) vs. placebo ("Cebocaps", Forest Pharmaceuticals, New York, NY) in a randomized single-blind crossover fashion on separate days (study nurse was unblinded; patient and PI were blinded). The patients were seated in a chair during the data collection except during prescribed periods of standing. Brachial cuff BP and HR were measured with an automated vital signs monitor (Dinamap Vital Signs Monitor, Critikon Corp) and digitally acquired into a custom-designed database (Microsoft Access, Microsoft Corporation, Redmond, Wash). At time zero and immediately before every hour for 4 hours after study drug administration, each patient was asked to stand for 10 minutes while standing HR and BP were recorded. Although the degree of orthostatic stress is not as great when the subject is standing from a seated position compared with standing from a supine position, it provides a clinically relevant and reproducible scenario.

The study was done as a proof of concept pilot study. As such, it was single-blinded, but the PI was also blinded. Only the nurse administering the study drug was aware of its contents.

Symptoms

Patients were asked to self-report their symptom burden immediately before and at 2 and 4 hours after study drug administration using the Vanderbilt Orthostatic Symptom Score (VOSS).[16] The patients were asked to rate the severity of 9 symptoms on a scale of 0 to 10 (with 0 reflecting an absence of symptoms). The sum of the scores at each time point was used as a measure of symptom burden (lower score reflects reduced symptoms burden). The 9 symptoms were mental clouding, blurred vision, shortness of breath, rapid heartbeat, tremulousness, chest discomfort, headache, lightheadedness, and nausea. This symptom score has been used previously by our center[16,6] and these symptoms were chosen because they reflect common complaints of patients with POTS.

Statistical Analysis

Our primary end point was the standing HR 2 hours after study drug administration. The 2-hour time point was chosen because the peak plasma concentration of DDAVP occurs 0.9 to 1.5 hours after dosing, with antidiuretic effects beginning 1 hour after dosing.[13] The null

hypothesis was that standing HR would not be statistically different between the DDAVP day and the placebo day. The primary statistical analysis involved a paired t test that compared the standing HR at 2 hours after study drug administration between DDAVP and placebo.

Secondary analyses were performed with a paired t test to compare standing HR at other time points after study drug administration, sitting HR at each time point, delta HR (standing minus sitting) at the 2 time points, and the standing, sitting, and delta SBP at the 2 time points. Repeated-measures ANOVA were used to compare HR, SBP, and symptom scores over time on both the DDAVP and placebo days; the Greenhouse-Geisser correction to the degrees of freedom from these analyses was used to adjust for departures of the variance-covariance matrix from the sphericity assumption. Spearman correlations were performed, relating the change in standing heart rate and the change in individual symptom scores (from baseline to 2 hours). Values are reported as means and standard deviations unless otherwise noted. Probability values <0.05 were considered statistically significant, and all tests were 2-tailed. Statistical analyses were performed with SPSS for Windows (version 19.0, IBM Corporation). Prism for Windows 5 (version 5.02, GraphPad Software Inc.) was used for graphical presentation.

RESULTS

Patient Characteristics

Study inclusion criteria were met by 30 subjects with POTS (26 female; 37±12 years). All subjects underwent the paired administration of placebo and DDAVP.

The data from the baseline supine and standing study are presented in Table 1. The supine HR was 77±13 bpm and BP was 110±12/69±11 mmHg. The supine plasma norepinephrine and epinephrine values were within the normal range (norepinephrine <2.81 nmol/L [<475 pg/mL] and epinephrine <0.41 nmol/L [<75 pg/mL]), with the exception of 1 patient with a high supine norepinephrine level of 3.64 nmol/L (616 pg/mL).Upon standing, there was a significant increase in HR (127±18 bpm, P<0.001) and norepinephrine (5.30±2.96 nmol/L [897±500 pg/mL], P<0.001) compared with supine numbers. SBP (110±12 vs. 119±20 mm Hg, P=0.006) and DBP (69±11 vs. 74±12 mm Hg, P=0.005) also increased on standing.

Hourly Seated and Standing HR Measurements with DDAVP 0.2 mg vs. Placebo

The data for drug trials are presented in Table 2. Immediately before administration of the study drug, there was no difference in seated HR between placebo (86±12 bpm) and DDAVP (85±13 bpm; P=0.484). As seen in Figure 1A, the seated HR decreased over time for both placebo and drug groups (ANOVA P_{Time}=0.008). The drug group also had a separate significant decrease in HR (ANOVA P_{Int} value 0.048).

The standing HR before study drug administration was not significantly different between placebo and DDAVP (117±16 vs. 112±18 bpm, P=0.054; Figure 1B). Both placebo and drug groups had a significant decrease in HR over the 4 hour time period (ANOVA P_{Time}<0.001). Compared with placebo, DDAVP effected a larger decrease in the standing HR (ANOVA P_{Int}<0.001). DDAVP effected a lower standing HR at 2 hours (P<0.001), which was the primary outcome measure, as well as at 1 hour (P<0.001), 3 hours (P=0.002), and 4 hours (P=0.027).

Before study drug administration, the POTS patients had a large postural increase in HR with standing (delta HR [ΔHR]), which is a cardinal feature of the POTS syndrome (DDAVP day 27±15 vs. placebo day 31±13 bpm, P=0.059). There was a significant

decrease in ΔHR over time for both groups (ANOVA P_{Time} <0.001.) DDAVP led to a significantly greater decrease in ΔHR than placebo (ANOVA P_{Int} =0.009.).

Seated and Standing BP Measurements with DDAVP 0.2 mg vs. Placebo

There were no differences in SBP (Figure 1C–D), DBP or MAP at baseline prior to study drug administration or while seated following study drug administration. With standing, there was a slight increase in SBP (Figure 1D), DBP, and MAP in both groups, but the differences were not significant and did not appear to be affected by study drug.

Symptoms

The symptom scores were completed for both study drug days by 15 patients with POTS (Figure 2). The symptoms ratings were similar between the DDAVP and placebo days prior to treatment (18±18 vs. 18±17 arbitrary units [AU], P=0.99). Placebo did not change symptom score in these patients (P=0.373), whereas DDAVP did lead to a significantly decreased symptom score (ANOVA P=0.010). The symptom score was significantly better with DDAVP than placebo at 2 hours (13±15 vs. 19±16 AU, P<0.001), coinciding with the primary hemodynamic endpoint, and at 4 hours (13±16 vs. 19±18 AU, P=0.006). This reflects a lower symptom burden with DDAVP over the testing period. The change in standing heart rate (0 to 2 hours) correlated with the change in Total Symptoms Score (Rs=0.44; P=0.058), although this did not reach statistical significance. Interestingly, there was a significant correlation for palpitation (Rs=0.52, P=0.023) and a strong, but non-significant trend for visual disturbance (Rs=0.41; P=0.086). The other symptoms had probability values for the correlation that were greater than P=0.1 (Figure 3).

DISCUSSION

POTS is a form of chronic orthostatic intolerance that leads to a significant decrease in quality of life. [17] Excessive orthostatic tachycardia in response to standing up from a lying position is the most obvious physiologic abnormality in POTS patients. One treatment strategy is to increase the circulating blood volume acutely.

We found that over 4 hours from the time of administration, DDAVP (1) significantly decreased the standing HR of patient with POTS; (2) significantly decreased orthostatic tachycardia; and (3) improved symptoms compared with placebo.

DDAVP Reduces HR

Oral DDAVP 0.2 mg caused a significant decrease in the standing HR within 1 hour of administration, and this effect persisted for at least 4 hours (Figure 1). These data provide a proof of concept for the idea of using DDAVP to restrain standing tachycardia in POTS. DDAVP also decreased seated HR in patients with POTS over time. This "tachycardia restraint" occurred without a significant change in BP, suggesting that it was not primarily due to a reflex decrease secondary to a primary increase in BP. Rather, it is more likely that the lower HR are due to an acute DDAVP-induced increase in blood volume.

This effect is distinct from the effect of vasopressin on hemodynamics. Vasopressin acts on the V1a receptor (which has both direct vasoconstriction effects and sympathetically mediated vasoconstriction) [18] and the V2 receptor (which has a free water retention effect mediated by the kidneys). Modifications of desmopressin result in significantly reduced smooth muscle contraction and vasopressor properties but increased antidiuretic function compared with vasopressin.[13] Given this, we would not expect significant sympathetic vasoconstrictive effects from desmopressin.

Decreased HR with Placebo Effects

The standing HR decreased even with the placebo intervention in POTS patients. While this has been noted in prior studies,[6,16] the reasons for this "time effect" are not clear. One possibility is that the POTS patients may experience a "psychological benefit" from thinking that they are receiving active therapy (patients were blinded to treatment allocation). This could lead to less anxiety and a reduction in HR. This potential placebo effect, however, was not reflected in the symptoms score. More likely, it is also possible that both the seated and standing HR physiologically decrease from early morning to midday. We have recently reported that there is a "diurnal variability" in orthostatic and standing tachycardia, with a peak early in the morning.[19] Importantly, despite the "time effect", DDAVP decreased the seated and standing HR significantly more than did placebo. This represents a strength of the present study.

Symptom Burden

There was a significant improvement in symptom burden in POTS patients who received DDAVP (Figure 2). Despite the HR response of the placebo group, placebo did not improve the symptom burden of the POTS patients. The improvement in symptoms score was significantly greater with DDAVP than placebo from baseline to 2 hours after study drug (coinciding with the primary hemodynamic endpoint) and out to 4 hours. The change in the Total Symptoms score and palpitation scores correlated with change in standing heart rate, while the change in visual disturbance score had a strong but non-significant trend. These data suggest that the improvement in these symptoms (for palpitations and possibly for visual disturbances) is related to the improvement in standing heart rate. The reasons for this are not clear, but could perhaps relate to reduced or altered cerebral perfusion with increasing tachycardia.

Blood Volume Expansion: DDAVP vs. Fludrocortisone

We[15] and others[20] have shown that patients with POTS have deficits in blood volume compared to controls. DDAVP is one of many strategies that could potentially improve this deficit acutely. By increasing free water reabsorption, DDAVP could potentially acutely expand the circulating plasma volume. Fludrocortisone, an aldosterone analogue, is commonly used for the treatment of POTS. The putative mechanism of action of fludrocortisone is increased sodium retention and plasma volume expansion. Potential side-effects of fludrocortisone include hypokalemia, hypomagnesemia, worsening headaches, acne, and fluid retention with edema.[11] Fludrocortisone has been used as a daily or twice daily medication, but the evidence for effectiveness is lacking and the increase in plasma volume may be transient.[12] DDAVP has been used in a slightly different manner. Anecdotally, DDAVP has been used successfully as an occasional "as needed" medication that effects an acute improvement in symptoms. At this time, we would not recommend DDAVP as a daily medication for POTS patients until safety studies are done. To date, we have used it as a 3rd line medication in treatment-refractory patients.

Safety Concerns about DDAVP

Potential side-effects of DDAVP include hyponatremia, edema and headache, given that DDAVP works to increase free-water retention.[13] Hyponatremia, in particular, is a side-effect that would be of significant concern with daily dosing. It should be noted that DDAVP has been used for years as a treatment for primary nocturnal enuresis in children with a very low rate of complications. Unlike enuresis patients, POTS patients are advised to consume significant amounts of free water. In this trial, patients with POTS were given single-dose, acute treatment only and there were no reported adverse effects (although plasma sodium was not measured after study drug administration). In the clinic, we have

been hesitant to prescribe this as a daily medication to patients with POTS due to the risk of hyponatremia. Several patients have safely used DDAVP in a "pill in the pocket" manner. They are allowed to use DDAVP no more than once a week for the acute improvement of symptoms. This is often used for "special occasions" or outings. These patients have anecdotally reported similar symptom improvement as was seen in this trial. They were instructed to have their serum sodium checked on a regular basis for hyponatremia, and we have not heard about laboratory abnormalities or other side effects in these patients.

DDAVP is also used as an acute treatment in Hemophilia A and won Willebrand Disease for the management of spontaneous or traumatic bleeding episodes. In otherwise healthy patients, there is not a known significant increase in factor VIII/vWF activity.[13] Desmopressin is renally cleared and studies on IV dosing have shown a significantly increased half-life with renal impairment. This would likely not be an issue with low-dose oral administration but is a theoretical risk.

Study Limitations

The main limitation of this study is the relatively small sample of patients. Although the sample size was not large, our primary outcome of reduction in standing HR was highly significant ($P<0.001$). The small sample size should bias against a significant finding, but our finding was significant. This emphasizes the large signal (with little noise) of the DDAVP data.

The time window of follow-up was quite short in this study. A time period of 4 hours makes it difficult to predict the long-term efficacy of this treatment. However, the study was able to show a "proof of concept" for the acute use of DDAVP for the control of tachycardia in POTS patients. This study did not address the long-term safety and tolerability of DDAVP in this population, especially in terms of hyponatremia. This cannot be determined without a well-powered, long-term, outpatient clinical trial.

Conclusions

DDAVP is highly effective at acutely decreasing orthostatic tachycardia and standing tachycardia in patients with POTS, and this was associated with an improvement in symptom burden in these patients. Longer-term studies are needed to assess this therapy.

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Glossary of abbreviations

AU	Arbitrary Units
bpm	Beats Per Minute
DDAVP	Desmopressin
DBP	Diastolic Blood Pressure
HR	Heart Rate

MAP	Mean Arterial Pressure
POTS	Postural Orthostatic Tachycardia Syndrome
SBP	Systolic Blood Pressure

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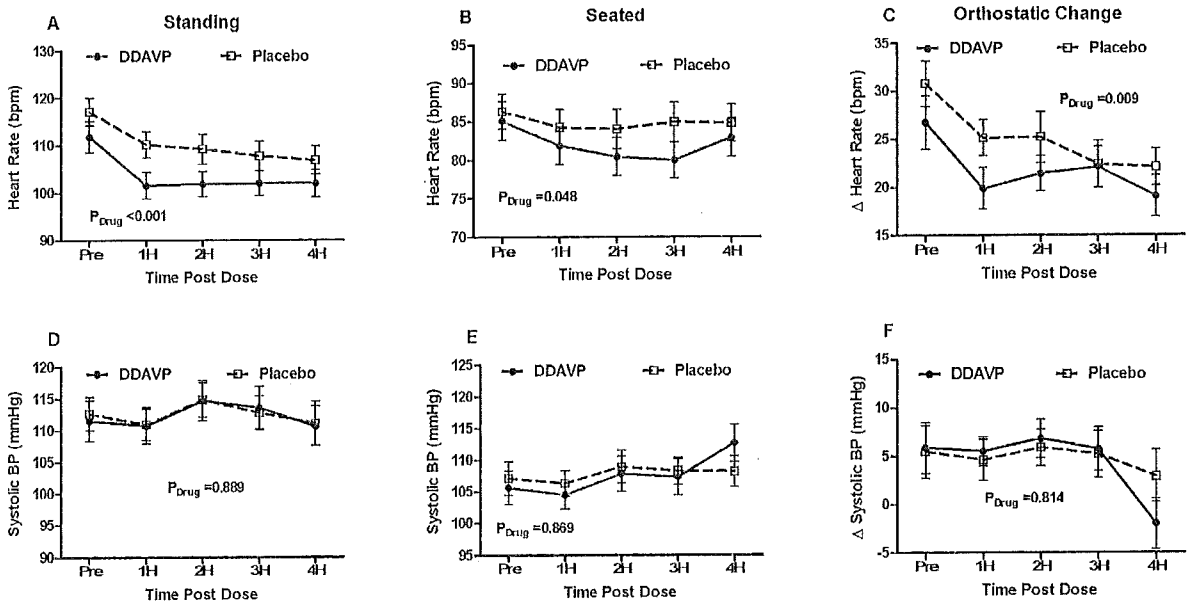

Figure 1. Seated, standing and orthostatic changes in heart rates and blood pressures before and after DDAVP 0.2 mg vs. placebo

Heart rate (HR) and systolic blood pressure (SBP) data are presented immediately before (pre), and hourly for 4 hours (4H) following study drug administration for the DDAVP 0.2 mg day ("DDAVP"; solid circles) and the placebo day (open squares). Peak HR after standing for a maximum of 10 minutes (Fig 1A), seated HR immediately before standing (Fig 1B) and the changes in HR from sit to stand (Fig 1C) are shown in the top 3 panels. Similarly, the data for standing SBP (Fig 1D), seated SBP (Fig 1E) and the changes in SBP from sit to stand (Fig 1F) are shown in the bottom 3 panels. The error bars represent the standard error of the mean. The ANOVA P values are presented for the overall effect of the study drug over time. bpm – beats per minute; mmHg – millimeters of mercury.

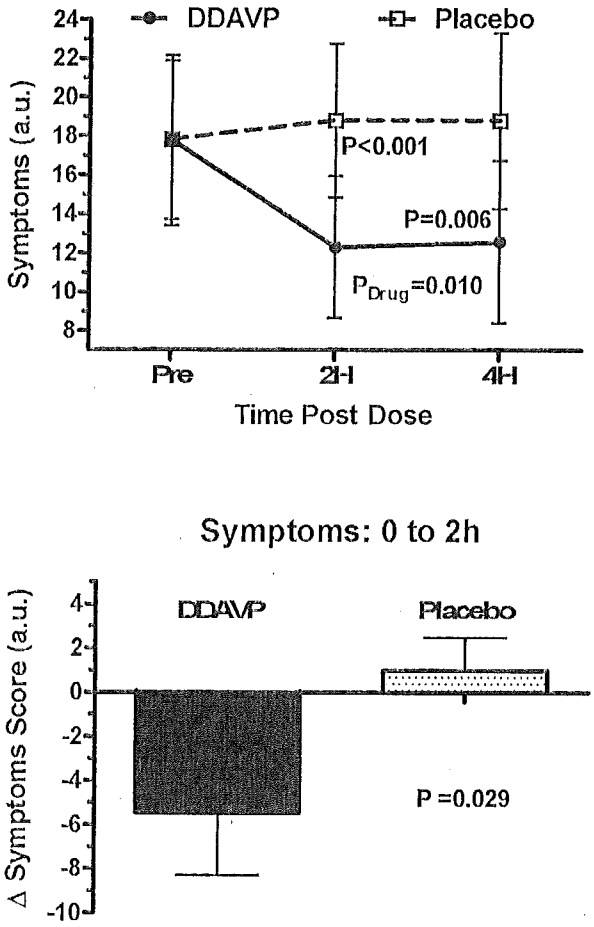

Figure 2. Change in symptoms with study medication

The changes in the total Vanderbilt POTS symptom score (in arbitrary units [au]) are presented from immediately before to 4 hours following study drug administration. **Top Panel**: Symptom scores are shown at baseline, at 2 hours, and at 4 hours for the DDAVP 0.2 mg day (black circles) and the placebo day (clear squares) for the 15 subjects that completed symptom reporting for both interventions. The P values at 2 and 4 hours were generated using Wilcoxon rank-sum tests, and the overall P_{Drug} using repeated measures ANOVA. **Bottom Panel**: The change in symptoms score from baseline to 2 hours after medication administration for the DDAVP 0.2 mg day (black bar) and the placebo day (clear bar) for the 15 subjects. A negative score reflects a reduction in symptom burden. The error bars represent standard error of the mean. The P value was generated using a Wilcoxon rank-sum test.

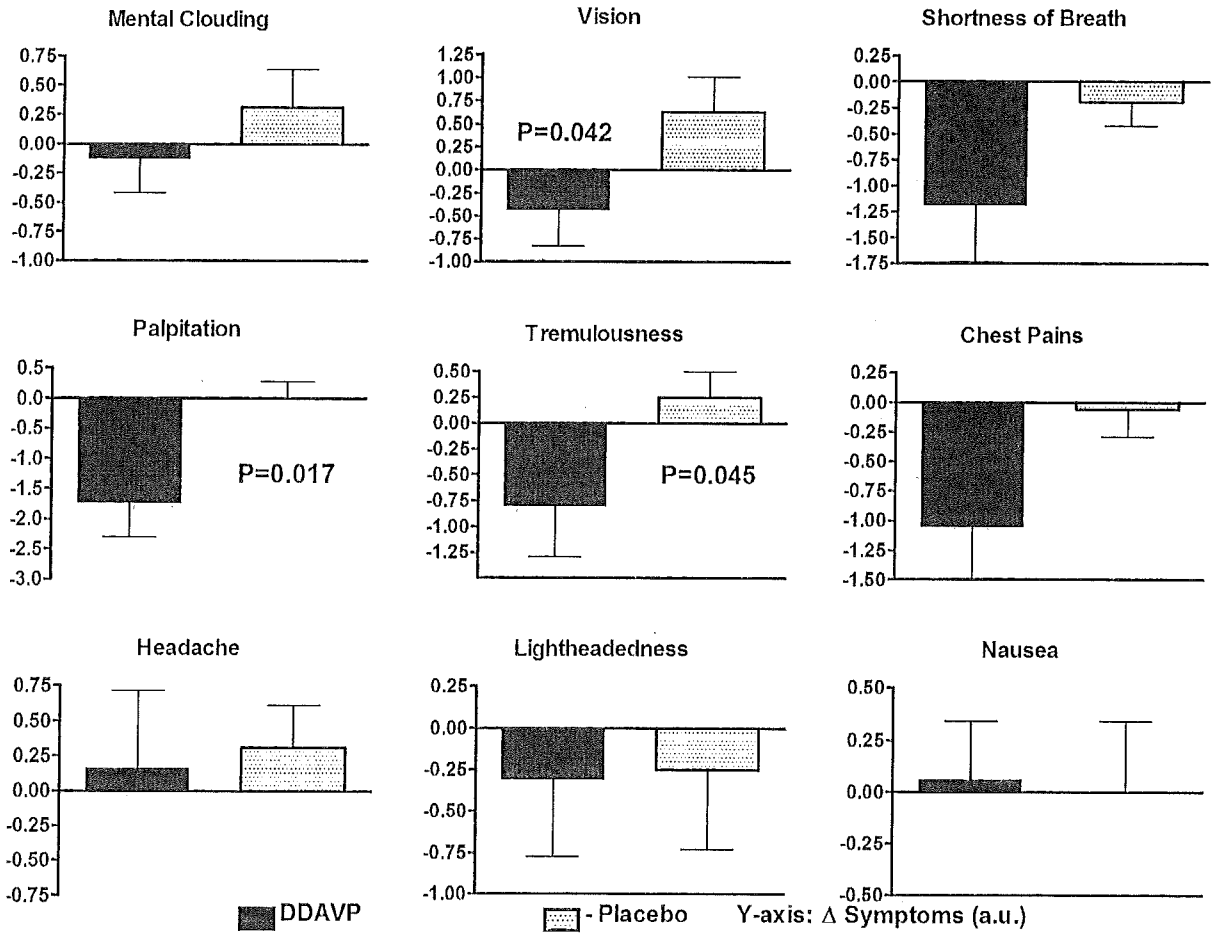

Figure 3. Changes in individual symptoms

The changes in the 9 individual components of the Vanderbilt POTS symptom score (in arbitrary units [au]) are presented from immediately before to 2 and 4 hours following study drug administration for DDAVP 0.2 mg (black bars) and placebo (clear bars). A negative number represents an improvement in symptoms.

Table 1

Baseline demographics, and postural vital signs and catecholamines of the subjects with Postural Tachycardia Syndrome (n=30).

Female (n)	26 (87%)		
Age (years)	37 ± 11		
Supine			
Heart Rate (bpm)	77 ± 13		
Systolic Blood Pressure (mmHg)	110 ± 12		
Diastolic Blood Pressure (mmHg)	69 ± 11		
Norepinephrine (nmol/L and pg/ml)	1.61 ± 0.86	272 ± 27	
Epinephrine (nmol/L and pg/ml)	0.16 ± 0.19	29 ± 35	
Standing			
Heart Rate (bpm)	127 ± 18		**
Systolic Blood Pressure (mmHg)	119 ± 20		*
Diastolic Blood Pressure (mmHg)	74 ± 12		*
Norepinephrine (nmol/L and pg/ml)	5.30 ± 2.96	897 ± 500	**
Epinephrine (nmol/L and pg/ml)	0.34 ± 0.26	62 ± 47	*
Change from Supine to Standing			
Heart Rate (bpm)	49 ± 18		
Systolic Blood Pressure (mmHg)	8 ± 15		
Diastolic Blood Pressure (mmHg)	5 ± 8		
Norepinephrine (nmol/L and pg/ml)	3.70 ± 2.42	625 ± 410	
Epinephrine (nmol/L and pg/ml)	0.18 ± 0.05	33 ± 9	

Bpm – beats per minute. Data are presented as the mean ± standard deviation. Reported P values are for paired t-tests comparing supine and upright parameters.

*P<0.05;

**P<0.001

Table 2

Orthostatic hemodynamics and symptoms with DDAVP and placebo in patients with Postural Tachycardia Syndrome (n=30).

	Pre	2 Hours Post	4 Hours Post	RM ANOVA P_{Drug} Value
Standing HR (bpm)				
DDAVP 0.2 mg	111.8 ± 17.8	101.9 ± 14.5	102.0 ± 15.9	
Placebo	117.1 ± 16.0	109.2 ± 17.4	106.8 ± 16.1	
P value (between drugs)	0.070	0.001	0.006	<0.001
Seated HR (bpm)				
DDAVP 0.2 mg	85.1 ± 13.5	80.4 ± 13.3	82.9 ± 13.8	
Placebo	86.3 ± 12.4	84.0 ± 14.0	84.7 ± 13.3	
P value (between drugs)	0.414	0.034	0.219	0.048
Delta (Standing-Seated) HR (bpm)				
DDAVP 0.2 mg	27.4 ± 15.4	21.1 ± 10.1	20.2 ± 10.2	
Placebo	31.1 ± 13.0	25.3 ± 14.7	22.4 ± 10.5	
P value (between drugs)	0.176	0.133	0.181	0.009
Standing SBP (mmHg)				
DDAVP 0.2 mg	111.5 ± 17.9	114.7 ± 17.2	110.6 ± 17.1	
Placebo	112.6 ± 14.2	114.8 ± 14.7	111.1 ± 19.0	
P value (between drugs)	0.640	0.770	0.853	0.889
Sitting SBP (mmHg)				
DDAVP 0.2mg	105.7 ± 14.7	107.8 ± 15.2	112.6 ± 16.0	
Placebo	107.2 ± 14.4	108.9 ± 14.2	108.2 ± 13.2	
P value (between drugs)	0.640	0.770	0.853	0.869
Delta (Standing-Seated) SBP (mmHg)				
DDAVP 0.2 mg	5.7 ± 15.2	5.8 ± 10.8	−0.2 ± 13.6	
Placebo	5.0 ± 15.2	5.4 ± 10.4	2.6 ± 15.5	
P value (between drugs)	0.984	0.866	0.247	0.814
Symptom Score (au) [n=15]				
DDAVP 0.2 mg	18 ± 18	13 ± 15	13 ± 16	
Placebo	18 ± 17	19 ± 16	19 ± 18	
P value (between drugs)	0.587	0.001	0.009	0.010

HR – heart rate; bpm – beats per minute; SBP – systolic blood pressure; au – arbitrary units; NS – not significant. Repeated measures analysis of variance (RM ANOVA) was used to determine the P value for the overall change between study drug and placebo and paired comparisons were made with the Wilcoxon Signed Rank test for paired data. Data are presented as mean±standard deviation. P<0.05 was considered significant.