Desmopressin acutely decreases tachycardia and improves symptoms in the postural tachycardia syndrome

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BACKGROUND Postural tachycardia syndrome (POTS) induces disabling chronic orthostatic intolerance with an excessive increase in heart rate on standing, and many patients with POTS have low blood volume. Increasing blood volume is a promising approach to this problem.

OBJECTIVE To test 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, heart rate, 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 The standing heart rate was significantly lower following DDAVP than placebo (101.9 ± 14.5 beats/min vs 109.2 ± 17.4 beats/min; $P < .001$). Standing blood pressure was not affected ($P = .28$). The symptom burden improved with DDAVP (from a score of 18 ± 18 arbitrary units [AU] to 13 ± 15 AU at 2 hours) compared with placebo (from 18 ± 17 AU to 19 ± 16 AU; $P = .010$).

CONCLUSIONS Oral DDAVP 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.

KEYWORDS Tachycardia; Desmopressin; Autonomic nervous system; Blood volume; Drugs; Orthostatic intolerance

ABBREVIATIONS **ANOVA** = analysis of variance; **AU** = arbitrary units; **BP** = blood pressure; **DBP** = diastolic blood pressure; **DDAVP** = desmopressin; **HR** = heart rate; **POTS** = postural tachycardia syndrome; **SBP** = systolic BP

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Introduction

Postural tachycardia syndrome (POTS) is a chronic disorder of the autonomic nervous system characterized by excessive increase in heart rate (HR) on standing in the absence of orthostatic hypotension. It 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 patients with POTS is still evolving, and scant data exist to support it. Acutely, the rapid infusion of normal saline can reverse the orthostatic tachycardia.[10] On a chronic basis, patients with POTS 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 increase 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] It 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 adrenocorticotropic hormone 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 hypoth-

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esis that DDAVP would decrease orthostatic tachycardia and improve symptoms in patients with POTS.

Methods

Subjects

Patients with POTS referred to the Vanderbilt University Autonomic Dysfunction Center 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 of ≥30 beats/min within 10 minutes of standing in the absence of orthostatic hypotension (a fall in blood pressure [BP] of >20/10 mm Hg). 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 of sodium and 70 mEq of potassium per day. 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 because of potential extended hormonal effects. HR, systolic BP (SBP), diastolic BP (DBP), mean arterial pressure, 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 postvoid state. In this trial, patients with POTS were given DDAVP 0.2 mg (Teva Pharmaceuticals, Petah Tikva, 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 principal investigator 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 Company, Tampa, FL) and digitally acquired into a custom-designed database (Microsoft Access, Microsoft Corporation, Redmond, WA). 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 principal investigator 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 admin-

Table 1 Baseline demographics and postural vital signs and catecholamines of the subjects with postural tachycardia syndrome (n = 30)

Sex: Woman, n (%)	26 (87)
Age (y)	37 ± 11
Supine	
Heart rate (beats/min)	77 ± 13
Systolic blood pressure (mm Hg)	110 ± 12
Diastolic blood pressure (mm Hg)	69 ± 11
Norepinephrine (nmol/L and pg/mL)	1.61 ± 0.86 and 272 ± 27
Epinephrine (nmol/L and pg/mL)	0.16 ± 0.19 and 29 ± 35
Standing	
Heart rate (beats/min)	127 ± 18*
Systolic blood pressure (mm Hg)	119 ± 20†
Diastolic blood pressure (mm Hg)	74 ± 12†
Norepinephrine (nmol/L and pg/mL)	5.30 ± 2.96 and 897 ± 500*
Epinephrine (nmol/L and pg/mL)	0.34 ± 0.26 and 62 ± 47†
Change from supine to standing	
Heart rate (beats/min)	49 ± 18
Systolic blood pressure (mm Hg)	8 ± 15
Diastolic blood pressure (mm Hg)	5 ± 8
Norepinephrine (nmol/L and pg/mL)	3.70 ± 2.42 and 625 ± 410
Epinephrine (nmol/L and pg/mL)	0.18 ± 0.05 and 33 ± 9

Data are presented as mean ± standard deviation. Reported *P* values are for paired *t* tests comparing supine and upright parameters.
*$P < .001$.
†$P < .05$.