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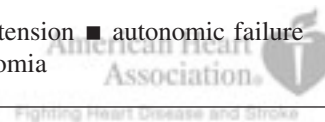
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Comparative Efficacy of Yohimbine Against Pyridostigmine for the Treatment of Orthostatic Hypotension in Autonomic Failure

Cyndya Shibao, Luis E. Okamoto, Alfredo Gamboa, Chang Yu, Andre' Diedrich, Satish R. Raj, David Robertson, Italo Biaggioni

Abstract—Orthostatic hypotension affects patients with autonomic failure producing considerable disability because of presyncopal symptoms. Severely affected patients may have residual sympathetic tone that can be engaged to increase blood pressure (BP) with the α -2 adrenergic antagonist yohimbine. This medication activates sympathetic outflow centrally and unrestrains norepinephrine release from noradrenergic neurons. Alternatively, the acetylcholinesterase inhibitor, pyridostigmine, can increase sympathetic tone by improving ganglionic cholinergic neurotransmission. Our purpose was to compare these complementary approaches and to explore whether the combination would lead to synergistic increases in BP. We compared the effects of 60 mg of pyridostigmine and 5.4 mg of yohimbine in a single-blind, randomized, placebo-controlled, crossover fashion. In a subset of patients we tested the combination of pyridostigmine and yohimbine. Our primary outcome was the change in standing diastolic BP 60 minutes after drug administration from baseline. We studied a total of 31 patients with severe autonomic failure. Yohimbine significantly improved standing diastolic BP as compared with placebo (11 ± 3 mm Hg [95% CI: 6 to 16 mm Hg]; $P < 0.001$). On the contrary, pyridostigmine did not increase the standing diastolic BP (0.6 ± 3 mm Hg [95% CI: -5 to 5 mm Hg]; $P = 0.823$). Only yohimbine showed a significant improvement in presyncopal symptoms. Sixteen patients received the combination of pyridostigmine and yohimbine, but no evidence of synergistic pressor effect was found. Engaging residual sympathetic tone with yohimbine is a more effective approach to improve orthostatic hypotension as compared with pyridostigmine in patients with severe orthostatic hypotension. (*Hypertension*. 2010;56:00-00.)

Key Words: pyridostigmine bromide ■ orthostatic hypotension ■ autonomic failure ■ autonomic drugs ■ dysautonomia



Severe orthostatic hypotension and presyncopal symptoms are the main cause of disability among patients with autonomic failure.¹ The current recommended therapeutic approaches are limited to medications that increase sodium reabsorption and expand plasma volume, such as fludrocortisones,^{2,3} or vasoactive agents, such as the α -1 adrenergic agonist midodrine.⁴⁻⁷ Although these interventions can effectively reduce symptoms related to orthostatic hypotension, in most cases they induce supine hypertension that further complicates their treatment.^{8,9} In this context, previous studies have reported the beneficial effect of pyridostigmine as an alternative therapy for orthostatic hypotension.^{10,11} Pyridostigmine inhibits the enzyme acetylcholinesterase and increases the transmission of impulses from cholinergic neurons across the synaptic cleft. Because the preganglionic sympathetic neuron is cholinergic, it is proposed to work as a facilitator of sympathetic ganglionic neurotransmission. While supine, the traffic to the autonomic ganglia is low,

whereas it is maximally activated during upright posture.¹¹ Therefore, this medication has the potential to increase vascular adrenergic tone only when engaged by upright posture, thus avoiding worsening of supine hypertension.¹² Although this mechanism of action appears ideal, the initial enthusiasm was damped by a recent report of poor improvement in standing blood pressure (BP).¹⁰ Alternatively, we have reported previously that yohimbine, an α -2 adrenergic receptor antagonist that enhances residual sympathetic tone, increases BP in autonomic failure patients and can be used as a possible therapeutic agent.¹³

In this study, we compared these 2 therapeutic approaches and tested the hypotheses that both yohimbine and pyridostigmine would be superior to placebo, and yohimbine would be superior to pyridostigmine on hemodynamic and symptoms parameters while standing. We also explored whether the combination of pyridostigmine with yohimbine would have any synergistic effect. We postulate that this effect could be

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This trial has been registered at www.clinicaltrials.gov (identifier NCT00223691).

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Table 1. Subject Characteristics

Diagnosis	Sex, Male/Female	BMI, kg/m ²	Age, y	Heart Rate, bpm		Norepinephrine, pg/mL	
				Supine	Upright	Supine	Upright
MSA	5/4	24.0±0.9	61.0±3.1	75.0±3.8	92.0±4.8	351.0±120.0	397.0±98.5
PAF	6/10	26.0±0.7	64.0±2.3	67.0±2.3	84.0±4.1	78.0±10.0	139.0±27.5
PD	3/3	27.0±2.1	70.0±3.3	79.0±7.2	91.0±10.3	287.0±138.9	491.0±279.5

particularly useful in patients severely affected with autonomic failure who may not benefit from the use of a single agent alone.

Methods

Subjects

A total of 31 patients with severe autonomic failure (9 with multiple system atrophy [MSA], 16 with pure autonomic failure [PAF], and 6 with Parkinson disease [PD]) were recruited from referrals to the Autonomic Dysfunction Center at Vanderbilt University. Orthostatic hypotension was defined as at least a 20-mm Hg decrease in systolic BP (SBP) or ≥ 10 mm Hg of diastolic BP (DBP) within 3 minutes on standing, according to the definition of the American Autonomic Society.¹⁴ Patients were excluded if they had secondary causes of autonomic failure (eg, diabetes mellitus or amyloidosis). The study was approved by the institutional review board at Vanderbilt University, and all of the subjects gave written informed consent.

The studies were conducted in the morning, 2.5 hours after meals and in a postvoid state to avoid any acute hemodynamic effects from eating. Patients were given a tablet of placebo, 60 mg of pyridostigmine (Valeant Pharmaceuticals International), or 5.4 mg of yohimbine (Goldline) in a randomized, single-blind, crossover fashion. In 16 patients we tested the combination of 60 mg of pyridostigmine and 5.4 mg of yohimbine.

The study was conducted with the patients seated on a chair with their feet on the floor. BP and heart rate (HR) were recorded every 5 minutes with an automated brachial BP cuff (Dinamap, Critikon) and digitally acquired into a custom-designed database (Microsoft Access, Microsoft Corporation). Baseline parameters were measured for 30 minutes, and orthostatic tolerance was tested by measuring BP and HR on standing. BP was measured for 60 minutes after drug administration. Assessment of orthostatic tolerance was repeated at the end of this period, as described above.

The change in standing DBP (Δ DBP) 60 minutes after drug administration from baseline was the primary outcome. Secondary outcomes include the orthostatic symptom score and the change in seated SBP and DBP 1 hour after drug administration. We selected DBP as the primary outcome because 2 previous studies^{10,11} used DBP as their main end point when reporting a significant improvement in BP with pyridostigmine.

Statistics

All data are presented as mean \pm SEM. For our primary analysis, we used paired *t* test to determine differences in the following comparisons: placebo versus yohimbine, placebo versus pyridostigmine, and pyridostigmine versus yohimbine. We used Bonferroni correction to adjust for multiple comparisons in the above 3 primary analyses. Our study had 80% power to detect an increase of 6 mm Hg in standing BP with pyridostigmine with an SD of 12, as reported previously in similar studies.¹⁰

In 16 patients, we performed exploratory analyses for the combination of pyridostigmine and yohimbine, and we used paired *t* test to determine differences in our primary outcome between each drug alone (placebo, yohimbine, and pyridostigmine) and the combination. We assessed the carryover effect by examining differences in the DBP at baseline before each intervention using 1-way ANOVA with repeated measures. Before and after comparison for the orthostatic symptoms score between treatments was tested using Wilcoxon

on signed-rank test. We also performed a subgroup analysis according to the level of the autonomic lesion. The treatment effect (drug-placebo) was compared in patients with central autonomic failure (MSA) versus those with peripheral autonomic failure (PAF and PD) using Wilcoxon rank-sum test. All of the tests were 2-tailed, and a *P* value of <0.05 was considered statistically significant. Analyses were performed with the SPSS statistical software (SPSS version 17.0, SPSS, Inc).

Results

Basal Cardiovascular and Autonomic Function

A total of 31 patients were studied, 17 were women and the average age was 66 ± 2 years. Patients with PD were ≈ 10 years older than those with PAF and MSA (Table 1). All subjects had a substantial decrease in systolic and DBP on standing ($-67 \pm 6 / -33 \pm 4$ mm Hg) without an adequate compensatory HR increase (16 ± 2 bpm). As expected, patients with MSA have higher supine plasma norepinephrine as compared with patients with PAF. No significant differences were found between MSA and PD in plasma catecholamines. The results of the autonomic function tests are presented in Table 2. The decrease in systolic BP during phase II of the Valsalva maneuver was exaggerated compared with responses in normal controls, and the SBP overshoot during phase IV was absent. The Valsalva ratio was low, indicating inadequate compensatory changes of HR. The pressor responses to isometric handgrip exercise or pain stimulus (cold pressor test) were impaired. Sinus arrhythmia was markedly reduced. Hence, autonomic testing indicated severe sympathetic and parasympathetic involvement.

Table 2. Autonomic Function Tests and Orthostatic Stress

Parameters	All Subjects	Normals†
Orthostatic change in SBP, mm Hg	-67.0 ± 5.7	≤ 20
Orthostatic change in HR, bpm	16.0 ± 2.1	≤ 20
Sinus arrhythmia ratio	1.07 ± 0.01	1.2 ± 0.1
SBP response to Valsalva in phase II, mm Hg	-58.0 ± 4.7	≤ 20
SBP response to Valsalva phase IV, mm Hg*	-31.0 ± 4.1	> 20
Valsalva ratio	1.10 ± 0.02	1.5 ± 0.2
Depressor response to hyperventilation, mm Hg	-34.0 ± 3.2	-5.0 ± 6.3
Pressor response to cold pressor, mm Hg	7.0 ± 1.7	24 ± 13
Pressor response to handgrip, mm Hg	1.7 ± 2.4	16 ± 6

*A negative value for phase IV of the Valsalva maneuver indicates that the BP overshoot was absent.

†Normal values are from the Autonomic Dysfunction Center Database at Vanderbilt University.

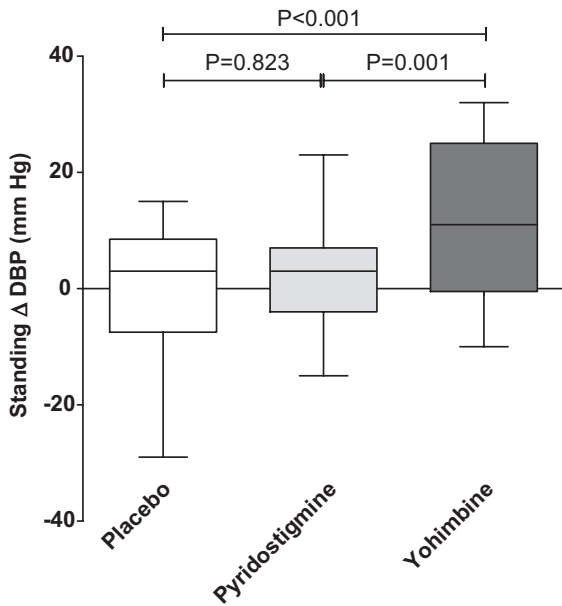


Figure 1. Changes in standing DBP 60 minutes after drug administration; there was a statistical significant difference between yohimbine vs placebo and yohimbine vs pyridostigmine ($P<0.001$ and $P=0.001$, respectively). No significant difference was found between pyridostigmine vs placebo.

Pressor Effect of Drugs

For our primary end point, we found that only yohimbine significantly increased standing DBP from baseline at 60 minutes after drug administration compared with placebo (Δ DBP 11 ± 3 mm Hg [95% CI: 6 to 16 mm Hg], $P<0.001$, significant using Bonferroni correction 0.05/3.00 for 3 comparisons). We did not find a significant increase in standing DBP from baseline with pyridostigmine (Δ DBP 0.6 ± 3.0 mm Hg [95% CI: -5.0 to 5.0]; $P=0.823$). There was a significantly increased in standing DBP with yohimbine compared with pyridostigmine (Δ DBP 9 ± 3 mm Hg [95% CI: 4 to 15]; $P=0.001$; $<0.05/3.00$; Figure 1).

In our exploratory analyses with 16 patients, the combination of pyridostigmine and yohimbine significantly increased standing DBP from baseline compared with placebo (Δ DBP 12 ± 4 mm Hg [95% CI: 4 to 19]; $P=0.006$) and pyridostigmine alone (Δ DBP 11 ± 3 mm Hg [95% CI: 4 to 17]; $P=0.003$). However, the combination of pyridostigmine and yohimbine did not significantly increased standing DBP compared with yohimbine alone (Δ DBP 3 ± 4 mm Hg [95% CI: -6 to 12]; $P=0.504$). Therefore, the pressor effect of the combination is driven mostly by yohimbine, and we were not able to demonstrate a synergistic effect on standing BP (Figure 2).

Regarding secondary end points, the magnitude of presyncope symptoms significantly improved after yohimbine alone ($P=0.006$). Neither pyridostigmine nor placebo experienced a significant improvement in presyncope symptoms (Figure 3). We found no differences in the standing DBP at baseline indicating that there was no carryover effect.

Seated SBP and DBP increased significantly during yohimbine as compared with placebo ($18 \pm 5.1/11 \pm 2.4$ versus $-1 \pm 4.2/1 \pm 2.7$, $P=0.007$ and $P=0.011$, respectively). As

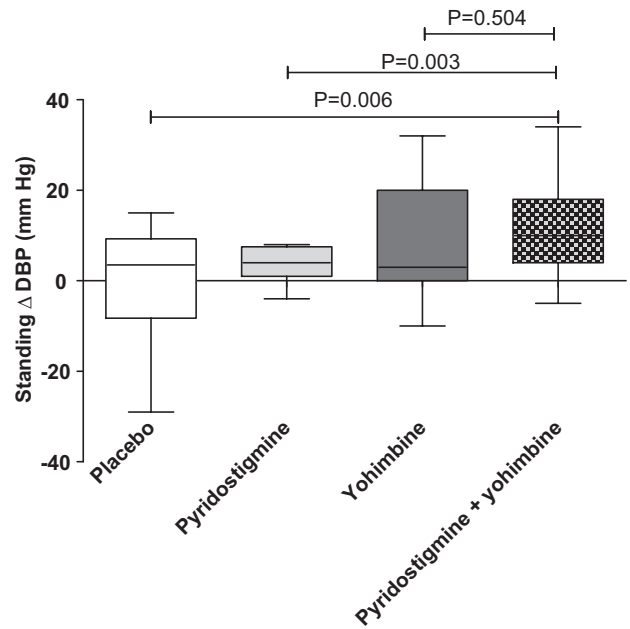


Figure 2. Changes in standing DBP 60 minutes after drug administration from baseline in 16 patients in whom we tried the combination of yohimbine and pyridostigmine; there was a significant difference between the combination vs placebo ($P=0.006$) and the combination vs pyridostigmine alone ($P=0.003$). There was no statistical significant difference between the combination and yohimbine alone.

reported previously, pyridostigmine did not increase seated BP significantly, indicating that without orthostatic stimuli pyridostigmine did not exert any pressor effect.

We analyzed the effect of seated SBP and DBP between patients with central versus those with peripheral autonomic failure. Patients with central autonomic failure had a statistically significant increase in seated BP with yohimbine as compared with those with peripheral autonomic failure. No significant differences in the effect of pyridostigmine between patients with central versus those with peripheral autonomic failure were found (Figure 4).

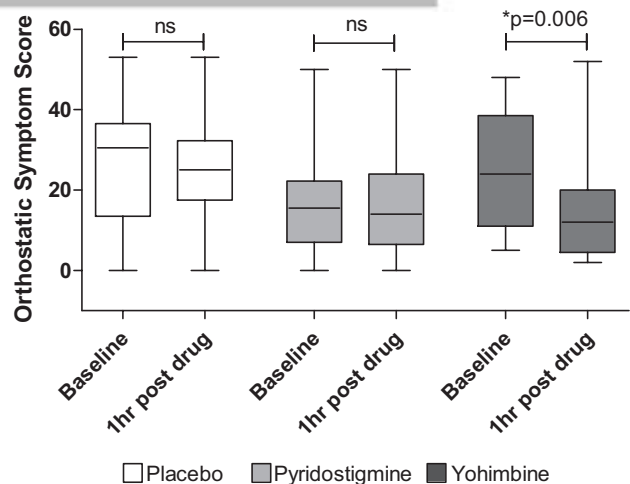


Figure 3. Orthostatic symptoms score at baseline and 1 hour postdrug administration. There was a significant decrease in presyncope symptoms only after yohimbine administration.

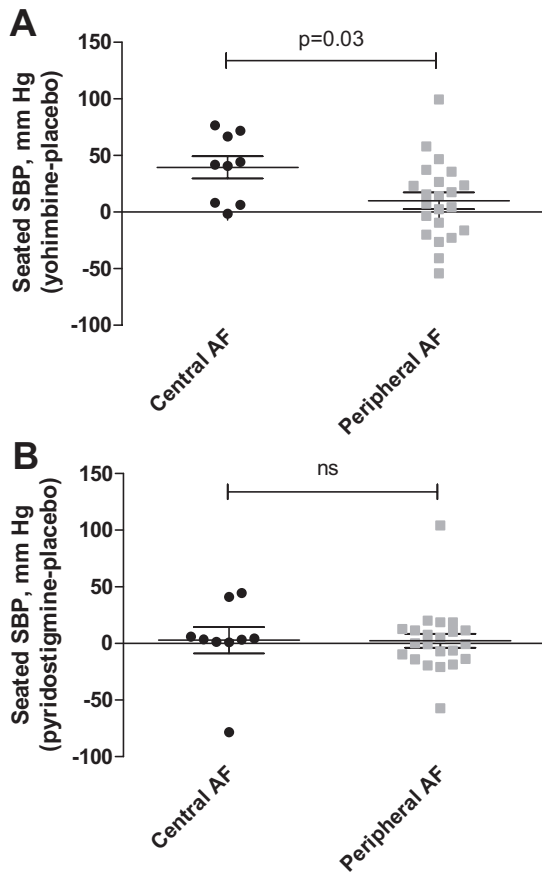


Figure 4. A, Treatment effect of yohimbine in patients with central autonomic failure (MSA) vs those with peripheral autonomic failure (PD and PAF). B, Treatment effect of pyridostigmine between patients with central vs peripheral autonomic failure.

Discussion

The main finding of this study is that targeting residual sympathetic tone with yohimbine, a central and peripheral adrenergic α -2 adrenergic antagonist, improves standing DBP and presyncopal symptoms in patients with severe autonomic failure. On the contrary, the pressor effect of pyridostigmine on standing BP was not different from placebo and was not sufficient to improve presyncopal symptoms in this group of patients. Furthermore, the combined use of yohimbine and pyridostigmine did not exert a significant synergistic effect on standing BP.

Yohimbine increases norepinephrine release from sympathetic nerves by augmenting central sympathetic outflow and by interfering with inhibitory modulation of presynaptic α -2 adrenoceptors. This translates into a pressor effect that can be used as a therapeutic approach in patients with autonomic failure.^{15,16} The pressor effect of yohimbine depends on the presence of residual sympathetic tone.¹⁵ Moreover, we found a statistically significant difference in the pressor effect with yohimbine depending on the level of the lesion. Patients with central autonomic failure (MSA) have intact efferent sympathetic nerves and had a greater pressor response than patients with peripheral autonomic failure (PAF and PD), who are affected by loss of efferent noradrenergic fibers. Previous studies have reported similar findings¹⁷; in patients with

peripheral autonomic failure, the pressor response to yohimbine has been shown to correlate with neuroimaging evidence for cardiac sympathetic denervation, as indicated by low concentration of 6-[¹⁸F] fluorodopamine-derived radioactivity in the interventricular septal myocardium. Even in this later group, the response to yohimbine varied significantly, supporting the hypothesis that the loss of autonomic function is incomplete in many patients with severe autonomic failure.¹⁸ On the other hand, some of the heterogeneity in response to yohimbine may be explained by interindividual differences in bioavailability of yohimbine, differences in receptor sensitivity to released norepinephrine, or blockade of vascular α -2-adrenoceptors.¹⁹ Of note, yohimbine had no pressor effects in cases of autonomic failure because of dopamine- β -hydroxylase deficiency,²⁰ presumably because there is no norepinephrine in the neurons of these patients.

Two previous studies have reported the beneficial effect of pyridostigmine as a treatment for orthostatic hypotension in patients with autonomic failure. The effect of pyridostigmine on standing DBP was first tested in an open label study¹¹ and then in a double-blind, randomized 4-way crossover study.¹⁰ Pyridostigmine facilitates sympathetic ganglionic neurotransmission, which is cholinergic. The appeal of this pharmacological approach is that it will be silent under conditions of low sympathetic tone, such as in the supine posture, but will potentiate the sympathetic activation that occurs on standing. This drug has the potential, therefore, to improve orthostatic BP without worsening supine hypertension. In apparent disagreement with previous published studies, we found that the magnitude of the increase in standing BP produced by pyridostigmine was not different from placebo, and this explains the lack of improvement in presyncopal symptoms. Furthermore, no differences were found in the pressor effect of pyridostigmine between central versus peripheral autonomic failure. Our results would seem to challenge the concept that pyridostigmine is beneficial for the treatment of orthostatic hypotension in autonomic failure patients. It should be noted, however, that our cohorts of patients were more severely affected by autonomic impairment than those recruited in previous studies; the average decrease in systolic BP reported by Singer et al¹¹ was \approx 44 mm Hg, whereas in our population the average decrease was \approx 60 mm Hg. Thus, it is possible that a significant effect could be achieved in less severe patients with greater autonomic “reserve,” as would be expected by the proposed mechanism of action of pyridostigmine.

We hypothesized that the combination of pyridostigmine and yohimbine would result in a synergistic pressor effect, given their distinct and complementary sites of action. This, however, was not the case. It is possible that residual sympathetic tone was maximally activated with yohimbine in these patients so that an additional effect of pyridostigmine was not apparent. It remains possible that a synergistic benefit of this combination could be apparent in patients with less severe autonomic failure.

Perspectives

This is the first study to compare the effects of yohimbine and pyridostigmine and the combination on BP in patients with

severe autonomic failure. Both drugs act by engaging residual sympathetic tone, producing a pressor effect in patients with autonomic failure. Our results support the concept that the loss of autonomic failure is incomplete in patients with autonomic failure, suggesting that this mechanism is an important therapeutic target.

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Disclosures

None.

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