Serotonin Reuptake Inhibitor (Paxil) Does Not Prevent the Vasovagal Reaction Associated With Carotid Sinus Massage and/or Lower Body Negative Pressure in Healthy Volunteers

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Background—The purpose of this study was to assess the effect of the serotonin reuptake inhibitor paroxetine hydrochloride (Paxil, SmithKline Beecham) on cardiovascular reflexes. We hypothesized that Paxil prevents neurally mediated syncope (NMS) by attenuating the sympathoinhibition and vagotonia associated with a vasovagal reaction.

Methods and Results—In a double-blind randomized study, 25 healthy subjects with a positive response to either carotid sinus massage (CSM) or lower body negative pressure (LBNP) received Paxil (20 mg/d) or placebo for 6 weeks. Arterial baroreflex sensitivity (BRS), muscle sympathetic nerve activity (SNA), baroreflex control of SNA, blood pressure, and heart rate responses to CSM and LBNP were measured at baseline and at 6 weeks. Nineteen subjects completed the study (Paxil, n=9; placebo, n=10). In the Paxil group, BRS decreased significantly compared with baseline (15.8±4.0 ms/mm Hg versus 11.0±2.6 ms/mm Hg, P=0.05); however, all 9 subjects continued to have a positive response to LBNP with presyncope. Paxil did not attenuate the sympathoinhibition or vagotonia associated with a positive LBNP response and had no significant effect on baroreflex control of SNA. In the control group, no significant change in BRS was noted compared with baseline. Seven out of 9 subjects who had a positive LBNP response at baseline had a repeat positive LBNP response, and the subject with a positive CSM at baseline had a negative response at 6 weeks.

Conclusions—Paxil decreases arterial BRS but does not prevent the presyncope associated with LBNP. The effect of Paxil on the autonomic reflexes in patients with neurally mediated syncope remains unclear. (Circulation. 2002;106:1500-1504.)

Key Words: nervous system, autonomic □ baroreceptors □ syncope

Neurally mediated syncope (NMS) is a common clinical problem that accounts for an estimated 3% to 5% of all emergency room visits and 1% to 6% of all hospitals admissions.1-4 The pathophysiological mechanism underlying NMS is not completely understood. The currently held hypothesis involves activation of unmyelinated c-fibers in the ventricles in response to orthostatic stress, resulting in centrally mediated sympathetic withdrawal and vagotonia. The outcome is bradycardia and/or vascular dilatation that often lead to syncope.

Clinical studies using selective serotonin reuptake inhibitors (SSRIs) in NMS have shown promising results.5-7 Recently, Girolamo et al5 demonstrated the effectiveness of paroxetine hydrochloride (Paxil, SmithKline Beecham) in reducing tilt and recurrent syncope in patients with refractory NMS. The postulated mechanism of action is an increase in central serotonin levels, which results in down-regulation of serotonin receptors, and thus attenuates any short-term, sudden shifts in central serotonin levels. This hypothesis however, has not been proven in humans.

The purpose of the present study was to assess the effect of the serotonin reuptake inhibitor Paxil on cardiovascular reflexes. Twenty-five subjects with a positive response to carotid sinus massage (CSM) or lower body negative pressure (LBNP) were randomized in a double-blinded fashion to either Paxil or placebo for 6 weeks. Arterial baroreflex sensitivity (BRS), muscle sympathetic nerve activity (SNA), baroreflex control of SNA, blood pressure, and heart rate responses to CSM and LBNP were measured at baseline and after 6 weeks of treatment or placebo. We hypothesized that Paxil prevents NMS by attenuating the sympathoinhibition and vagotonia associated with a vasovagal reaction.

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Baseline HR, BP and SNA (n=42)

Nitroprusside/Phenylephrine injection (NTP/PE)

Carotid sinus massage (CSM)

Lower body negative pressure (LBNP) for a total of 30 minutes

Positive response to CSM and/or LBNP (n=25)

Randomization

Figure 1. Summary of the protocol.

Methods

Subjects
The study was performed at the Dallas Veterans Affairs Medical Center and was approved by the institutional review board. Informed consent was obtained from all patients, and all procedures were in accordance with institutional guidelines. Healthy volunteers with no known history of cardiovascular, neurological, or psychiatric illnesses were asked to enroll. Subjects taking monoamine oxidase inhibitors or serotonin reuptake inhibitors were excluded. Forty-two subjects were enrolled in the study. Of these, 25 had a positive response to either CSM or LBNP and thus proceeded into the randomization arm of the study.

Measurements
BRS was calculated as the slope of the relationship of the change in the R-R interval to the change in systolic blood pressure (ms/mm Hg) after sodium nitroprusside and phenylephrine bolus infusions. Efferent post-ganglionic muscle SNA was recorded from the right peroneal nerve as previously described.8,9 Briefly, a sterile microelectrode was inserted into a fascicle of the peroneal nerve near the fibular head. The nerve signals were amplified, filtered (700 to 2000 Hz), rectified, and discriminated. Raw nerve signals were integrated (time constant=0.1 seconds) to produce a mean voltage display for quantitative analysis. SNA was calculated as total activity derived from the sum of the amplitude of SNA bursts during a 30 second period and was expressed as a percentage of baseline. Baroreflex control of SNA was calculated as the slope of the relationship of change in SNA (percent of baseline value) to change in diastolic blood pressure (%/mm Hg) after sodium nitroprusside and phenylephrine bolus infusions. Blood pressure (BP) was obtained non-invasively using photoplethysmography (Finapres model 2300, Ohmeda). Heart rate (HR) was derived from continuous ECG recordings. All data were recorded continuously to a hard disk for off-line analysis with the use of computerized analog-to-digital conversion hardware and software (Windaq, Dataq Inst).

Experimental Protocol
Subjects were studied in a drug-free postabsorptive state. On arrival to the laboratory, an antecubital peripheral intravenous catheter was placed for drug administration. After obtaining acceptable SNA, BP, and HR recordings, the following protocol (Figure 1) was performed: baseline recordings were taken for 3 minutes; nitroprusside/phenylephrine (NTP/PE) was injected; patients recovered for 5 minutes; baseline recordings were taken for 3 minutes; carotid sinus massage was performed; patients recovered for 5 minutes; baseline recordings were taken for 3 minutes; lower body negative pressure was performed for a total of 30 minutes; and patients recovered for 5 minutes.

Nitroprusside/Phenylephrine Injection
Sodium nitroprusside was administered in graded bolus of 50, 100, or 200 μg until a decrease in systolic BP of >10 mm Hg was achieved. Phenylephrine hydrochloride was then administered in graded bolus of 50, 100, or 200 μg at the nadir of the BP drop until an increase in systolic BP >10 mm Hg above baseline was achieved.

Carotid Sinus Massage
CSM was performed with the patient in the supine position, the neck hyperextended and the head turned away from the side being tested. The carotid impulse was gently felt and pressure was applied firmly for approximately 5 to 10 seconds on one side and then the other. A positive CSM response was defined as a 10 mm Hg decrease in systolic BP associated with sympatheoinhibition or vagotonia.

Lower Body Negative Pressure
LBNP was performed with the patient in a supine position, with the lower half of the body enclosed in a semi-ar t-tight chamber. Negative pressure was applied with the use of a commercial vacuum cleaner in a graded fashion starting at −10 mm Hg and increasing by 10 mm Hg every 2 minutes (3 minutes in the first 4 subjects) until −60 mm Hg was reached. After reaching −60 mm Hg, LBNP was continued until a positive response was noted or 30 minutes elapsed. A positive response was defined as an abrupt drop in systolic BP (>10 mm Hg over 30 seconds) associated with sympatheoinhibition or vagotonia.

Statistical Analysis
Data were recorded using Windaq data acquisition software on a personal computer and analyzed with customized software. Comparisons between groups were made by use of Student’s t test. Statistical significance was defined as P≤0.05. All data are presented as mean±SEM.

Results
Subjects’ Characteristics
Twenty-five subjects had a positive response to CSM or LBNP and were randomized to Paxil or placebo. Five subjects dropped out of the study; 3 subjects had nonspecific symptoms (nausea, dry mouth, and headache, n=1; constipation and headache, n=1; and extreme fatigue, n=1). 1 subject did not complete the follow-up phase, and another subject did not complete the study because of technical difficulties with the LBNP chamber. In addition, 1 subject in the control arm had a therapeutic blood level for paroxetine hydrochloride for unknown reasons and was thus eliminated from the study. In the remaining 19 subjects, 9 were randomized to Paxil and 10 to placebo. The 2 groups were not statistically different in terms of age and sex. Similarly, baseline HR, BP, and SNA values were not statistically different. A summary of the baseline data is provided in Table 1.

Baseline Studies
In the Paxil group, all 9 subjects had a positive LBNP response, whereas none had a positive response to CSM. During LBNP, all subjects experienced presyncope and symptoms common to NMS, including lightheadedness, diaphoresis, tunnel vision, and nausea. The mean time to
The 30 seconds preceding presyncope were not significantly different compared with baseline (SNA = 212 ± 66% versus 217 ± 75%; HR = 85 ± 9 versus 89 ± 9 bpm, P = NS). Furthermore, time to presyncope was not different at baseline compared with repeat LBNP at 6 weeks (17.3 ± 1.7 minutes at baseline versus 18.5 ± 1.4 minutes at 6 weeks, P = NS). In the control group, 7 of 9 subjects who had a positive LBNP response at baseline had a positive response during repeat LBNP, and the only subject who had a positive CSM at baseline had a negative response at 6 weeks. The time to a positive LBNP response was not significantly different at 6 weeks compared with baseline (20.1 ± 1.5 minutes at baseline versus 20.8 ± 2.4 minutes at 6 weeks, P = NS). A summary of the CSM and LBNP responses at baseline and at 6 weeks is provided in Table 2.

Blood was drawn to measure paroxetine hydrochloride levels in all 19 subjects. In 1 of the 9 subjects in the Paxil group, the drug level could not be measured because of a problem with the blood collection. In the remaining 8 subjects, the mean blood level was 31 ± 6 ng/mL (therapeutic >20 ng/mL).

**Discussion**

The main finding of this study is that the serotonin reuptake inhibitor Paxil decreases arterial baroreflex sensitivity but does not prevent the presyncope associated with LBNP. In addition, Paxil had no significant effect on baroreflex control of SNA. To our knowledge, this is the first study to assess the effect of any SSRI on cardiovascular reflexes and the sympathoinhibition and vagotonia associated with a vasovagal reaction in humans. Our findings suggest that although Paxil may have an effect on baroreflex sensitivity, it does not prevent vasovagal reactions in healthy volunteers. The effect of this drug on the autonomic reflexes in subjects with a history of NMS remains unclear.

**Previous Animal Studies**

A number of neurotransmitters have been postulated to be involved in neurally mediated blood pressure regulation, including catecholamines, opioid peptides, arginine-vasopressin, nitric oxide, adenosine, and 5-hydroxytryptamine or serotonin (5-HT).10–12 Since the pioneering work of Dahlstrom and Flux,13 serotonin has emerged as a neurotransmitter with a prominent role in blood pressure regulation. In cats, the intracerebroventricular injection of serotonin produces a decrease in heart rate, blood pressure,
and sympathetic activity that resembles the sympathetic withdrawal seen in neurocardiogenic syncope. Pretreatment with a centrally acting decarboxylase inhibitor that blocks the conversion of 5-hydroxytryptophan to serotonin eliminates this depressor effect. Morgan et al demonstrated that serotonergic blockers prevented the renal sympathoinhibitory response that occurred during hypotensive hemorrhage in rats. Recognizing that hemorrhage might increase the synthesis and release of serotonin and thereby the activation of vagal afferent reflexes, the authors concluded that serotonergic mechanisms are critically involved in the vagal afferent inhibition of renal SNA. Finally, Abboud also reported that central intracerebroventricular serotonin induces hypotension, inhibition of renal SNA, and excitation of adrenal sympathetic nerve activity. On the basis of these animal studies, several investigators have examined the usefulness of serotonin reuptake inhibitors as a therapy for neurally mediated cardiovascular disorders.

The Role of SSRIs in Neurally Mediated Cardiovascular Disorders

In humans, it seems that activation of cerebral serotonin receptors produces a depressor effect that is primarily due to sympathoinhibition. Accordingly, the role of this neurotransmitter in cardiovascular disorders that involve neurally mediated hypotension and bradycardia has received great interest. In particular, SSRIs have been used as a therapy in chronic orthostatic hypotension, carotid sinus hypersensitivity, and NMS. Grubb et al evaluated the usefulness of fluoxetine hydrochloride, a selective SSRI, in 16 patients with recurrent syncope and a positive tilt-table test. Three patients were intolerant of the medication. In the remaining 13 patients, 7 had a negative repeat tilt test and remained asymptomatic over a mean follow-up period of 19±9 months. Similarly, in another study from the same group, 9 of 14 patients who tolerated sertraline hydrochloride had a negative repeat tilt table testing and remained symptom free over a mean follow-up period of 12±5 months. Both studies were nonrandomized and enrolled a small number of patients. A recent study by Di Girolamo et al assessed the effect of paroxetine hydrochloride in 68 consecutive patients with recurrent syncope and tilt table testing in whom standard therapies failed. Patients randomly received either Paxil at 20 mg/d or a placebo. After 1 month of treatment, 61.8% of patients receiving Paxil had a negative repeat tilt table testing versus 38.2% in the placebo group (P<0.00001). The authors concluded that Paxil significantly improved the symptoms of patients with vasovagal syncope and is well tolerated.

Present Study

In the present study, the administration of Paxil did not prevent presyncope or attenuate the sympathoinhibitory or vagotonia associated with LBNP. We believe our findings are different from previous studies because of the subjects enrolled. Unlike previous studies, only healthy volunteers were asked to participate. The effect of Paxil on BRS and the autonomic reflexes in patients with a history of NMS remains unknown. Other possible explanations for the discrepancy

### TABLE 2. Effect of Paxil on CSM and LBNP Response

<table>
<thead>
<tr>
<th></th>
<th>Control (n=10)</th>
<th>Paxil (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>6 Weeks</td>
</tr>
<tr>
<td>+ CSM/ + LBNP</td>
<td>1/9</td>
<td>0/7</td>
</tr>
<tr>
<td>Time to + response, min</td>
<td>20.1±1.5</td>
<td>20.8±2.4</td>
</tr>
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+ indicates positive.
between our findings and previous studies include the amount of drug used and the possibility of poor compliance in the Paxil group. We chose 20 mg of Paxil because this was the dose used in the only randomized controlled trial\(^7\) that showed a beneficial effect of this drug on tilt induced and spontaneous syncope in subjects with NMS. Although poor compliance cannot be excluded, we believe this was unlikely because a therapeutic blood level was achieved in the Paxil group and a decrease in BRS was demonstrated, suggesting the presence of a drug effect.

Possible mechanisms for the decrease in BRS noted with Paxil use include increased intrasynaptic serotonin levels with secondary postsynaptic serotonin receptor downregulation and increased intrasynaptic serotonin levels with feedback inhibition of further presynaptic release. The lack of a drug effect on resting SNA and baroreflex control of sympathetic activity suggests that Paxil may have different effects on sympathetic and parasympathetic motor neurons.

Furthermore, because reflex sympathoexcitation plays a major role in determining the hemodynamic response to orthostatic stress,\(^20\)–\(^22\) the absence of a significant change in baroreflex control of SNA might explain why Paxil failed to prevent presyncope in our subjects.

**Limitations**

This study has limitations. First, the study involved only healthy volunteers without a history of NMS. The effect of Paxil on BRS and autonomic reflexes in patients with NMS remain unknown. Second, 3 of the 10 subjects in the control arm had a negative repeat CSM or LBNP test at 6 weeks, when no therapy was given. We believe this is due to an inherent limitation of these procedures and constitutes the rationale for conducting randomized trials when such tests are used in the assessment of any therapy for NMS. Finally, our findings might have been different if we had used a larger number of subjects. Although this possibility cannot be ruled out, the absence of a repeat negative LBNP test in all 9 subjects receiving Paxil makes this unlikely.

**Conclusion**

In conclusion, we found that Paxil did not alter the neural response to graded orthostatic stress in subjects with a demonstrated susceptibility for presyncope, but it did attenuate arterial baroreflex control of HR during transient changes in BP. Despite this modest attenuation of baroreflex control of HR, BP maintenance during orthostatic stress was not compromised before the onset of presyncope. Moreover, we found that Paxil did not have a significant effect on resting SNA or baroreflex control of sympathetic activity. The different effects of Paxil on baroreflex control of HR and SNA suggest that the mechanism of action on baroreflex control is most likely mediated within the brain stem, and that there may be a differential role of serotonin in controlling sympathetic and parasympathetic motor neurons.

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**References**

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