Norepinephrine Transporter Blockade With Atomoxetine Induces Hypertension in Patients With Impaired Autonomic Function

Cyndya Shibao, Satish R. Raj, Alfredo Gamboa, André Diedrich, Leena Choi, Bonnie K. Black, David Robertson, Italo Biaggioni

Abstract—Atomoxetine, a selective norepinephrine transporter blocker, could increase blood pressure by elevating norepinephrine concentration in peripheral sympathetic neurons. This effect may be masked in healthy subjects by central sympatholytic mechanisms. To test this hypothesis we studied the pressor effect of 18 mg of atomoxetine (pediatric dose) in 21 patients with damage of the central (10 subjects) and peripheral (11 subjects) autonomic nervous system. Atomoxetine was administered in a randomized, crossover, placebo-controlled fashion, and blood pressure and heart rate were measured at baseline and for 60 minutes after drug intake. Atomoxetine acutely increased seated and standing systolic blood pressure in patients with central autonomic failure by 54/26 (mean ± standard deviation; \( P = 0.004 \)) and 45/23 mm Hg (\( P = 0.016 \)), respectively, as compared with placebo. At the end of the observation period the mean seated systolic blood pressure in the atomoxetine group was in the hypertensive range (149 ± 26, range 113 to 209 mm Hg). However, in patients with peripheral autonomic failure, atomoxetine did not elicit a pressor response; seated and standing systolic blood pressure increased by 4 ± 18 mm Hg (\( P = 0.695 \)) and 0.6 ± 8 mm Hg (\( P = 0.546 \)) with atomoxetine as compared with placebo. In conclusion, atomoxetine induces a dramatic increase in blood pressure in patients with central autonomic failure even at very low doses. These findings suggest that a functional central sympatholytic pathway is essential to avoid hypertension in patients treated with this drug. Caution should be exercised when this medication is used in patients with milder form of autonomic impairment. (Hypertension. 2007;50:47-53.)

Key Words: atomoxetine ■ norepinephrine transporter protein ■ hypertension ■ autonomic nervous system diseases ■ multiple system atrophy

The selective norepinephrine transporter (NET) blocker atomoxetine is commonly used in the treatment of attention deficit hyperactivity disorder in children and adults.\(^1\)\(^2\) Its use is increasing in the United States, given the reportedly high prevalence of this disorder, affecting nearly 4% of US population.\(^3\) NET blockers are also used for the treatment of other common conditions such as obesity and depression. On this background, there is concern that this family of drugs could worsen or even induce hypertension.\(^4\) Indeed, blockade of norepinephrine reuptake would be expected to increase neurotransmitter concentrations in the neuro-effector junction, and in the periphery this effect would lead to a pressor response. This mechanism, however, seems to be counteracted by a central sympatholytic action through activation of \( \alpha \)-2 adrenoreceptors (a “clonidine-like” effect)\(^5\)\(^6\).

We proposed to dissect the effect of NET blockade in humans by determining the pressor response to atomoxetine in patients with distinct forms of autonomic impairment based on the level of the lesion; patients with multiple system atrophy (MSA) who have central autonomic impairment, and patients with pure autonomic failure (PAF) and Parkinson disease (PD+) with peripheral autonomic impairment. MSA patients lack central autonomic modulation but have intact postganglionic sympathetic fibers and residual sympathetic tone.\(^7\) In contrast, PAF and PD+ patients have low sympathetic tone because of postganglionic sympathetic denervation.\(^8\)\(^9\) We hypothesized that NET blockade will induce a pressor effect in patients with intact peripheral sympathetic fibers (MSA or central autonomic impairment), but not in patients with peripheral autonomic denervation.

Methods

Subjects
A total of 21 patients with severe autonomic failure (10 with central autonomic failure and 11 with peripheral autonomic failure) were recruited from referrals to the Autonomic Dysfunction Center at Vanderbilt University. Orthostatic hypotension was defined as at
least 20 mm Hg fall in systolic blood pressure within 3 minutes on standing, documented on multiple occasions. Patients were excluded if they had secondary causes of autonomic failure (eg, diabetes mellitus, amyloidosis) or if atomoxetine was contraindicated (eg, abnormal liver function, narrow-angle glaucoma). The criteria of the American Autonomic Society were used to differentiate between patients with PAF, PD, and SMA.10 The study was approved by the Institutional Review Board at Vanderbilt University and all subjects gave informed consent.

Procedures
All subjects were admitted to Vanderbilt University’s General Clinical Research Center. Subjects were fed a low-monoamine caffeine-free diet containing 150 mg sodium and 70 mg potassium per day, for at least 3 days before evaluation. Medications affecting the autonomic nervous system and blood volume, ie, fludrocortisone, were withheld for at least 5 half-lives before admission.

All participants went through an initial screening phase. Autonomic function tests were performed to evaluate the integrity of autonomic reflex arcs. These included the Valsalva maneuver, the cold pressor test, isometric handgrip, and sinus arrhythmia (change in heart rate in response to controlled breathing).11 All tests were previously standardized in our laboratory.12 An orthostatic test was performed to evaluate hemodynamic and hormonal changes on standing. An indwelling catheter was placed in an antecubital vein to obtain blood samples while patients remained supine after an overnight rest. Subjects were asked to stand as long as possible or for up to 10 minutes. During this period, they were allowed to sit at intervals if presyncopal symptoms developed. Brachial blood pressure and heart rate were measured using an automated brachial sphygmomanometer (Dinamap, GE Medical Systems Information Technologies, Milwaukee, Wis) medium size, placed on the right arm, and blood samples for catecholamine determinations were obtained while supine and standing. Plasma catecholamine levels (dihydroxyphenylglycol, norepinephrine) were determined by high-performance liquid chromatography with electrochemical detection.13 All the procedures followed were performed by trained research nurses and were followed in accordance with institutional guidelines.

Medication Trial
All the studies were conducted in the morning, 2.5 hours after breakfast to avoid any acute hemodynamic effects from eating, and in a postvoid state. On separate days, patients were given a pediatric dose of atomoxetine, 18 mg (Eli Lilly pharmaceuticals, Indianapolis, Ind), or placebo in a randomized, single-blind, crossover fashion. The study was conducted with the patients seated in a chair with their feet on the floor. Blood pressure and heart rate were recorded every 5 minutes with an automated brachial sphygmomanometer (Dinamap Critikon 1846SX, Tampa, Fla), medium size cuff, placed on the right arm. Data were 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 blood pressure and heart rate on standing. Blood pressure was measured for 60 minutes after drug administration, while peak plasma levels are achieved.14 Assessment of orthostatic tolerance was repeated at the end of this period, as described above. In 11 patients (6 with central autonomic failure and 5 with peripheral autonomic failure), plasma catecholamines were measured at the end of a 30-minute baseline period and 60 minutes after drug administration.

Statistics
All data are presented as mean±SD. The systolic blood pressure (SBP) measurements taken every 5 minutes for 60 minutes after drug administration were the primary outcome to examine the difference in the time courses between the atomoxetine day and the placebo day within each patient group (central and peripheral autonomic failure) or between the atomoxetine days for the 2 groups. A random effect model was used instead of ANOVA because it not only takes into account repeated measurements, but also the correlation between measurements taken over time within a subject. The model allowed for the determination of individual slopes for the atomoxetine day or the placebo day within each patient group. We adjusted for mean of baseline blood pressure measurements (calculated by taking the mean of 7 baseline measurements) in the model. The model also included adjustments for the sequence and period effects as potential confounding factors.

Secondary analyses included a comparison between the placebo and atomoxetine day in the following parameters: changes from baseline in seated SBP and standing SBP at 60 minutes, and absolute values for seated and standing SBP at 60 minutes. Differences in these responses between patients with peripheral autonomic failure and central autonomic failure were examined by using Mann–Whitney U test.

In addition, we determined whether there was a significant difference in plasma norepinephrine (NE) and the plasma dihydroxyphenylglycol to NE ratio at baseline and after the drug administration. All these analysis were performed by using Wilcoxon-signed rank test.

All tests were 2 tailed, and a probability value of <0.05 was considered significant. Analyses were performed with the SPSS statistical software (SPSS version 14.0, SPSS Inc), STATA 9.1 (StataCorp), and R (www.r-project.org).

Results
Basal Cardiovascular and Autonomic Function
Orthostatic cardiovascular and neurohumoral determinations are presented in Table 1. As expected, patients with central autonomic failure have higher supine plasma NE and were younger as compared with patients with peripheral autonomic failure (plasma NE 256±104 vs 74±47 pg/mL; age 62±9 versus 67±7 years old, P=0.003, P=0.06, respectively). There were no significant differences in body mass index, supine SBP, and orthostatic changes in SBP between groups (P=0.943 P=0.698, and P=0.860, respectively).

The results of the autonomic function tests are presented in Table 2. All patients have a profound decrease in blood pressure on standing without an adequate increase of heart rate. The decrease in systolic blood pressure during phase II of the Valsalva maneuver was exaggerated compared with responses in normal controls, and the systolic blood pressure overshoot during phase IV was absent. The Valsalva ratio was low, indicating inadequate compensatory changes of heart rate. 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.

Pressor Response to Atomoxetine
Systolic blood pressure during the atomoxetine day was significantly increased as a linear function of time compared with the placebo day in patients with central autonomic failure (slope difference between the atomoxetine and placebo days 0.92; 95% CI 0.73 to 1.11; P=0.001) whereas no statistically significant difference in time trend between the placebo day and the atomoxetine day was found for peripheral autonomic failure patients (slope difference between the atomoxetine and placebo days 0.16; 95% CI −0.02 to 0.34; P=0.08). In addition, the rate of increase in the time course of SBP during the atomoxetine day for central autonomic failure was significantly greater than during the atomoxetine day for peripheral autonomic failure (slope difference between groups in the atomox-
etine days 0.89; 95% CI 0.71 to 1.07; P = <0.001; Figure 1). Similar statistical differences were obtained if the general linear model ANOVA was used instead of the random effect model. In patients with central autonomic failure atomoxetine increased seated SBP by 54 ± 26 mm Hg at the end of the 60-minute trial (compared with 2 ± 13 mm Hg with placebo, \( P = 0.004 \)). At the end of the observation period the mean seated SBP was in the hypertensive range (149 ± 26, range 113 to 209 mm Hg). In contrast, in patients with peripheral autonomic failure, atomoxetine did not increase SBP at the end of the 60-minute trial (compared with 2 ± 13 mm Hg with placebo, \( P = 0.004 \)). At the end of the observation period the mean seated SBP was within the normotensive range (120 ± 7, range 94 to 139 mm Hg).

### TABLE 1. Subjects Clinical Characteristics

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<th>No.</th>
<th>Diagnosis</th>
<th>Gender</th>
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<th>Age (y)</th>
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<td>Mean ± SD+</td>
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<tr>
<td></td>
<td>Peripheral AF</td>
<td></td>
<td>20 ± 6</td>
<td>67 ± 7</td>
<td>74 ± 47</td>
<td>125 ± 143</td>
</tr>
</tbody>
</table>

BMI indicates body mass index.

*Data are presented as means with standard deviations.

### TABLE 2. Autonomic Function Tests and Orthostatic Stress in Patients With Peripheral and Central Autonomic Failure

<table>
<thead>
<tr>
<th>Parameters (Unit)</th>
<th>Central AF</th>
<th>Peripheral AF</th>
<th>Normals*</th>
</tr>
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<tr>
<td>Orthostatic change in systolic blood pressure, mm Hg</td>
<td>-60 ± 27</td>
<td>-65 ± 36</td>
<td>±20</td>
</tr>
<tr>
<td>Orthostatic change in heart rate, beats per minute</td>
<td>12 ± 8</td>
<td>13 ± 10</td>
<td>5–10</td>
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<tr>
<td>Sinus arrhythmia ratio†</td>
<td>1.09 ± 0.05</td>
<td>1.05 ± 0.04</td>
<td>1.2 ± 0.1</td>
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<tr>
<td>Depressor response to Valsalva in phase II, mm Hg</td>
<td>-64 ± 28</td>
<td>-63 ± 24</td>
<td>±20</td>
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<tr>
<td>Blood pressure response to Valsalva phase IV, mm Hg‡</td>
<td>-39 ± 25</td>
<td>-43 ± 30</td>
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<tr>
<td>Valsalva ratio</td>
<td>1.03 ± 0.06</td>
<td>1.1 ± 0.1</td>
<td>1.5 ± 0.2</td>
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<td>Depressor response to hyperventilation, mm Hg</td>
<td>-24 ± 24</td>
<td>-29 ± 16</td>
<td>-5 ± 6.3</td>
</tr>
<tr>
<td>Pressor response to cold pressor, mm Hg</td>
<td>10 ± 11</td>
<td>7 ± 7</td>
<td>24 ± 13</td>
</tr>
<tr>
<td>Pressor response to handgrip, mm Hg</td>
<td>0.9 ± 15</td>
<td>-1 ± 12</td>
<td>16 ± 6</td>
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</table>

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

†The ratio between the highest and lowest heart rate during 6 cycles of deep breathing.

‡A negative value for phase IV of the Valsalva maneuver indicates that the blood pressure overshoot was absent.
not elicit a pressor response (change in seated SBP of 4±18, compared with −1.1±17 with placebo, *P=0.695).

In central autonomic failure, there was an increase in upright SBP with atomoxetine as compared with placebo (45±23 versus 2±17 mm Hg, *P=0.016, respectively). At the end of the trial absolute values for upright systolic and diastolic blood pressures were 112±29 and 72±15 mm Hg, respectively, in the atomoxetine group, compared with 76±18 and 50±12 mm Hg in the placebo group (Figure 2). In patients with peripheral autonomic failure, no changes were observed in upright SBP with atomoxetine as compared with placebo (0.6±8 versus 5±11 mm Hg, *P=0.546, respectively). Individual values for the changes in SBP induced by atomoxetine in patients with central and peripheral autonomic failure are shown in Figure 3.

**Neurohumoral Changes**

Plasma catecholamines were measured in the seated position at baseline and 60 minutes after administration of atomoxetine in 6 patients with central autonomic failure and 5 patients with peripheral autonomic failure. In patients with central autonomic failure plasma NE tended to increase with atomoxetine (from 317±143 pg/mL at baseline to 430±83 pg/mL after atomoxetine, *P=0.06). On the contrary, plasma NE in patients with peripheral autonomic failure did not change with atomoxetine (from 81±65 pg/mL at baseline to 78±72 pg/mL, *P=0.84). The ratio dihydroxyphenylglycol/NE, an index of NET function,15 tended to decrease with atomoxetine in central autonomic failure (from 5±2 at baseline to 3±1 with atomoxetine, *P=0.09) but not in patients with peripheral autonomic failure (from 12±5 at baseline to 12±4 with atomoxetine, *P=0.84).

**Discussion**

Our main finding is that blockade of the norepinephrine transporter with extremely low doses of atomoxetine induces hypertension in patients with central autonomic failure, but not in those with peripheral autonomic failure. Three important clinical implications can be derived from these findings. First, our results suggest that intact central autonomic function is essential in preventing hypertension in patients in whom the use of atomoxetine is indicated. Secondly,
Atomoxetine has therapeutic potential in patients with central lesions. Thirdly, the response to atomoxetine can provide insight about the level of the lesion in autonomic disorders. Previous studies have shown that norepinephrine transporter blockers in normal subjects produce only a minimal, if any, increase in blood pressure. This is surprising given that blockade of norepinephrine would increase its synaptic concentration and therefore potentiate its action in the peripheral sympathetic neurons. A tentative explanation for these findings is that this peripheral sympathomimetic effect is compensated by other mechanisms. A central inhibition of the sympathetic nervous system produced by NET blockade activity has been suggested. Indeed, other norepinephrine transporter inhibitors such as reboxetine, or tricyclic antidepressants with NET blockade such as desipramine acutely decrease sympathetic outflow as measured by muscle sympathetic nerve activity. Orthostatic hypotension is a known side effect of tricyclic antidepressants, however it is not entirely clear to what extent NET blockade or a central sympatholytic effect plays a role in this phenomenon.

We used a different approach to explore the central and peripheral consequences of NET blockade by determining its hemodynamic effects in 2 pathophysiological models of autonomic nervous system function. Our findings of a striking increase in blood pressure in patients with central autonomic failure with preserved peripheral sympathetic neurons imply that this central activation plays a key role in the prevention of hypertension among users of NET blockers.

Our results raise safety concerns about the use of atomoxetine and other norepinephrine transporter blockers in the treatment of attention deficit hyperactivity disorder and many other common conditions such as obesity and depression. Treatment of adult patients with atomoxetine is routinely started with doses that are at least 2-fold higher dose than the pediatric dose that greatly increased blood pressure in our patients. It should be noted, however, that we studied patients with extreme cases of autonomic impairment in whom even an oral water bolus can elicit profound, albeit transient, pressor responses. In subjects with intact autonomic function, the central sympatholytic effects of atomoxetine appear to counteract its peripheral pressor effect. It has yet to be determined whether significant hypertension will arise in individuals with milder impairment of autonomic function, such as the elderly. It is reassuring that diabetic autonomic neuropathy, arguably the most common cause of autonomic impairment, is likely to produce a peripheral form of the disease unresponsive to the pressor effects of atomoxetine. Some patients, however, can present with a hyperadrenergic form, and may be at greater risk of developing hypertension with atomoxetine.

Conversely, the pressor effect of atomoxetine can be exploited therapeutically to improve the functional capacity of MSA patients with orthostatic hypotension, in cases not responsive to other pharmacological agents. Orthostatic blood

Figure 2. Seated and upright BP and heart rate 60 minutes after administration of placebo or 18 mg atomoxetine in patients with central autonomic failure (A) and peripheral autonomic failure (B).
pressure in such patients increased by nearly 50 mm Hg, a goal achieved by few other medications, including the alpha-2-adrenoreceptor antagonist yohimbine\textsuperscript{23} or the sympathomimetic phenylpropanolamine.\textsuperscript{24} Patients should use this drug at least 45 minutes before upright activities and avoid the supine position for 3 to 4 hours because their blood pressure will remain elevated throughout this period. Atomoxetine will not be useful in patients with peripheral autonomic disorders, but such patients may respond to direct α-adrenoreceptor agonists.

A common diagnostic challenge is the differentiation between patients with central autonomic failure (MSA) versus those with peripheral autonomic failure (PD+ and PAF).\textsuperscript{25} Because there is no curative treatment for these disorders, an accurate diagnosis is important mainly because of its prognostic value. On average, MSA patients have reduced life expectancy, with death occurring within 9 years of disease.\textsuperscript{26} In contrast, patients with peripheral autonomic failure syndromes have a better prognosis. A neurological examination is paramount in the differentiation of these conditions. However, in the early phase of the disease, when the neurological features of MSA may not be present, the diagnostic can be difficult.

Other functional abnormalities in central autonomic pathways that can be demonstrated in patients with MSA may be useful in their diagnosis; vasopressin levels do not increase in response to hypotension\textsuperscript{27} and growth hormone levels are not increased in response to clonidine,\textsuperscript{28} whereas its responses are preserved in other autonomic syndromes.\textsuperscript{9} On the other hand, MSA patients have intact postganglionic neurons as determined by normal or only slightly decreased plasma norepinephrine,\textsuperscript{13} normal or elevated low-frequency variability of blood pressure,\textsuperscript{29} and intact cardiac uptake of 6-[18F]fluorodopamine\textsuperscript{30} or [123I] metiodobenzylguanide (MIBG) determined by positron emission tomography or single photon emission computed tomography.\textsuperscript{31} In contrast, patients with peripheral autonomic failure have very low plasma norepinephrine,\textsuperscript{13} greatly decreased low-frequency variability of blood pressure,\textsuperscript{29} and absent uptake of 6-[18F]fluorodopamine by the heart,\textsuperscript{30} as would be expected from a loss of peripheral noradrenergic fibers. These tests have been helpful not only in improving our understanding of the underlying pathophysiology of these disorders, but also in their differential diagnosis. In this context, the pressor response to atomoxetine may add to the evidence about the level of the lesion of the autonomic nervous system. A substantial pressor response would argue in favor of a failure in the central autonomic pathways with preservation of peripheral autonomic nerves, whereas a negative response will suggest loss of peripheral noradrenergic nerve function. Nevertheless, a moderate pressor response is less useful because overlap exists between groups. Furthermore, it is important to note that none of the tests previously reported to differentiate between central and peripheral forms or autonomic disorders, nor the response to atomoxetine described here, have been rigorously validated in patients with initial stages of disease. Further research is required before any of these tests, including the response to atomoxetine, can be recommended as diagnostic tools in the differentiation of these disorders.

The observation that clonidine reduces blood pressure in MSA patients,\textsuperscript{32} whereas atomoxetine increases it, may provide insight about the pathophysiology of this condition. Clonidine is known to act as an agonist of α-2 adrenergic receptors in the central nervous system to reduce sympathetic tone, and this central effect is the likely the mechanism of action for the decrease in blood pressure produced by this agent in MSA patients, known to have residual sympathetic tone. This is supported by the observation that the lowering of blood pressure with clonidine in autonomic failure patients is associated with a decrease in sympathetic tone as determined by a reduction in plasma norepinephrine,\textsuperscript{33} and is proportional to the patients’ residual sympathetic tone as determined by their response to trimethaphan.\textsuperscript{32} On the other hand, for atomoxetine to reduce sympathetic tone, it requires a tonic presynaptic release of norepinephrine in relevant central nervous system centers, which appears to be greatly reduced in MSA patients. This leaves unopposed the peripheral pressor actions of atomoxetine, which depends on residual sympathetic outflow with tonic release of norepinephrine, known to be preserved in MSA. The precise site of the autonomic lesion that explains the cardiovascular alterations seen in MSA patients, however, has not been defined.

In conclusion, pediatric doses (18 mg PO) of atomoxetine produced a dramatic increase in blood pressure in patients with multiple system atrophy with central autonomic impairment but intact peripheral noradrenergic fibers. Atomoxetine improved standing blood pressure and may prove useful in the treatment of orthostatic hypotension in these patients. Pressor responses of such magnitude are not reported in normal subjects and are likely counteracted by a sympatholytic effect of norepinephrine reuptake that requires intact central autonomic pathways. This effect was not observed in patients with pure autonomic failure, raising the possibility that the response to atomoxetine can become a useful pharmacological tool in the differential diagnosis between central and peripheral autonomic disorders.

**Perspectives**

Norepinephrine transporter blockers are commonly used for the treatment of attention deficit disorder, obesity, and depression, conditions with high incidence in the United States. Because this family of drugs could enhance the sympathetic nervous system, there is a growing concern about their safety cardiovascular profile. Our findings, that pediatric doses of the selective NET blocker Atomoxetine have a profound pressor effect in patients with central autonomic failure, indicate that intact baroreflex pathways are essential in the prevention of hypertension associated with the use of NET blockers. Caution should be exercised when using these drugs, particularly in patients with milder forms of autonomic impairment.

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DISCLOSURES

None.

REFERENCES

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