Effect of Xamoterol in Shy-Drager Syndrome

Atsushi Obara, MD; Hirohisa Yamashita, MD; Sokichi Onodera, MD; Osamu Yahara, MD; Hajime Honda, MD; and Naoyuki Hasebe, MD

Background. Xamoterol, a cardioselective β1-adrenoceptor partial agonist, has been reported to be effective on postural hypotension. We investigated the effect of xamoterol in five patients with Shy-Drager syndrome (SDS) in relation to their prevailing sympathetic nerve activity and sensitivity of β-adrenoceptors and the change in circadian variation of blood pressure.

Methods and Results. Ambulatory blood pressure over 24 hours was monitored by noninvasive sphygmomanometer (model 5200, Spacelab). Plasma norepinephrine levels of SDS patients were significantly lower than that of normal subjects (n=5) both at rest (54±15 versus 178±83 pg/ml) and after 10-minute standing (74±24 versus 318±143 pg/ml). Infusion of isoproterenol (0.02 μg/kg/min) produced a mild rise of systolic blood pressure and tachycardia in normal subjects but resulted in marked hypotension and tachycardia in SDS subjects. After xamoterol administration (200 mg b.i.d.), systolic blood pressure and heart rate were significantly increased in the averages during the day; however, increases were more pronounced at night. In two of the five patients, the improvement in dizziness was large enough to enable them to increase their daily activities.

Conclusions. Our observations suggest that 1) β1-selective, high intrinsic sympathomimetic activity of xamoterol increases blood pressure and heart rate in patients with SDS as a consequence of their prevailing β1-adrenoceptor hypersensitive state, and 2) blood pressure monitoring over 24 hours appears to have important advantages in evaluating the therapeutic effects on postural hypotension. (Circulation 1992;85:606–611)

Shy-Drager syndrome (SDS) is a multisystem disease that gives rise to disorders of the autonomic nervous system, cerebellum, and extrapyramidal tracts. Various interventions, including salt loading, cardiac pacing, indomethacin, adrenocortical hormones, α-agonists, β-agonists, and β-antagonists, have been attempted to treat postural hypotension, the most severe symptom in patients with SDS. In recent years, xamoterol, a β1-selective partial agonist, has been reported to be effective on postural hypotension.1 We also reported previously that xamoterol increased casual blood pressure and decreased episodes of fainting in patients with SDS2; however, the mechanism of the effects remained unclear. Mann3 demonstrated a consistent circadian trend in blood pressure of patients with postural hypotension, with the lowest pressure in the morning and the highest at night, and found a correlation of the nadir of the blood pressure measurements with the reported time of peak incidence of orthostatic symptoms. Moreover, their large swings of blood pressure values are known to show hypertensive levels exacerbated by treatment.4 Therefore, blood pressure monitoring over 24 hours appears to have important advantages in evaluating the therapeutic effects on postural hypotension.

In this study, to clarify the mechanism of xamoterol effects on patients with SDS, we examined their endogenous catecholamine status and β-adrenoceptor sensitivity in comparison with five normal subjects. To interpret the effects of xamoterol administration (200 mg b.i.d.) on circadian variations of blood pressure and heart rate, we monitored the SDS patients for 24 hours with the use of a noninvasive ambulatory sphygmomanometer.

Subjects

We studied five inpatients with SDS (all men, 64±10 years old) and five normal volunteers (all men, 59±14 years old). The clinical features of the patients with SDS are briefly described below and in Table 1. They all exhibited severe postural hypotension5 at 1 minute after standing up (Table 2). The possible diagnoses of diabetes mellitus, amyloidosis, Addison's disease, porphyria, or heavy metal toxicity were eliminated.

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TABLE 1. Clinical Features of Patients With Shy-Drager Syndrome

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
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<tr>
<td>Age (years)</td>
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<td>65</td>
<td>55</td>
<td>61</td>
<td>60</td>
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<tr>
<td>Duration of symptoms (years)</td>
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<td>2</td>
<td>3</td>
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<td>4</td>
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<td>+*</td>
<td>+</td>
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<tr>
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<tr>
<td>Impotence</td>
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<td>0</td>
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</tbody>
</table>

All patients were men. +, Present; 0, absent; *first symptom.

Case 1. This 73-year-old man noticed difficulty in micturition at the age of 71. Two years later, he noted the first dizziness on rising from a sitting position. Neurological examination revealed dysmetria, dysdiadochokinesis, decreased gag reflex, lowering of the tone of his voice, and muscle wasting of the extremities. The next year, he developed dysphagia, left brisk reflexes, and an equivocal plantar response on the right side.

Case 2. This 65-year-old man was hospitalized because of difficulty in walking, writing, and speaking, and urinary incontinence, which all had developed gradually during the preceding 2 years. On admission to our hospital, he was fully oriented, but speech was slurred. Gross dysmetria on nose-finger test, poor rapid alternating movements, muscle wasting of the legs, resting finger tremor, and rigidity of the extremities were noted.

Case 3. A 55-year-old man was admitted with complaints of progressive constipation, hesitance in urination, impotence, lack of sweating, and severe orthostatic dizziness, all for 3 years. On neurological examination, he was found to have ataxia of the trunk, dysdiadochokinesis, dysmetria on nose-finger test, decreased gag reflex, dysarthria, dysphagia, and bilateral extensor plantar responses.

Case 4. This man was in good health until the age of 58 years, when he noted faintness and dizziness on standing from the sitting position. The following year, he noticed difficulty in walking, which had worsened gradually. On admission, when he was 61 years old, neurological examination showed dysdiadochokinesis, dysmetria on nose-finger and heel-knee tests, decreased gag reflex, dysarthria, dysphagia, mild rigidity of the right wrist, and muscle wasting of the extremities. During subsequent hospitalization, he developed hyperreflexia, equivocal extensor plantar response bilaterally, and generalized rigidity.

Case 5. This man was well until the age of 56 years, when he noticed difficulty in micturition. During the next 4 years, he developed constipation, impotence, and dizziness on standing from the sitting position, and then was admitted to our hospital. Neurological examination showed generalized rigidity, muscle wasting of the extremities, dysarthria, and right finger tremor.

TABLE 2. Plasma Norepinephrine and Xamoterol Effects in Patients With Shy-Drager Syndrome

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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</thead>
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<tr>
<td>Plasma NE concentration (pg/ml)</td>
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<td></td>
<td></td>
<td></td>
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<td>Supine position</td>
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<td>40</td>
<td>55</td>
<td>43</td>
<td>53</td>
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<tr>
<td>Standing position</td>
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<td>76</td>
<td>56</td>
<td>—</td>
<td>56</td>
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<td>Supine (control period)</td>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>SBP/DBP (mm Hg)</td>
<td>178/72</td>
<td>125/80</td>
<td>128/78</td>
<td>115/70</td>
<td>110/67</td>
</tr>
<tr>
<td>HR (beats per minute)</td>
<td>64</td>
<td>68</td>
<td>70</td>
<td>67</td>
<td>71</td>
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<td>Standing (control period)</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>SBP/DBP (mm Hg)</td>
<td>60/-</td>
<td>90/57</td>
<td>86/60</td>
<td>67/-</td>
<td>66/41</td>
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<tr>
<td>HR (beats per minute)</td>
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<td>73</td>
<td>70</td>
<td>68</td>
<td>70</td>
</tr>
<tr>
<td>Supine (xamoterol treatment period)</td>
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<td></td>
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<td>SBP/DBP (mm Hg)</td>
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<td>154/95</td>
<td>166/104</td>
<td>132/76</td>
<td>146/94</td>
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<td>HR (beats per minute)</td>
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<td>76</td>
<td>99</td>
<td>90</td>
<td>82</td>
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<tr>
<td>Standing (xamoterol treatment period)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP/DBP (mm Hg)</td>
<td>90/46</td>
<td>109/57</td>
<td>138/87</td>
<td>76/-</td>
<td>113/82</td>
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<tr>
<td>HR (beats per minute)</td>
<td>79</td>
<td>81</td>
<td>105</td>
<td>92</td>
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<td>Syncopeal attacks (per week)</td>
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<tr>
<td>Control period</td>
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</tr>
<tr>
<td>Xamoterol treatment period</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

NE, norepinephrine; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; —, unmeasurable.
Methods

Endogenous and Exogenous Catecholamine Status

Endogenous catecholamine level and β-adrenoceptor sensitivity were studied in the 10 subjects, all of whom were free of any drugs affecting blood pressure for at least 1 week. Plasma norepinephrine (NE) concentration was measured after 15 minutes of rest in the supine position and 10 minutes after standing up. This study could not be completed in case 4 because the patient was unable to continue standing (Table 2); this subject was rested again in the supine position, and after blood pressure and heart rate were stable, 0.02 μg/kg/min of isoproterenol diluted with physiological saline was infused intravenously. Blood pressure and heart rate were measured every minute through this study by an automatic sphygmomanometer (Nihon Kohrin BP-103N), and steady-state values before infusion and 5 minutes after infusion of isoproterenol were evaluated.

Plasma NE concentration was measured by modified high-performance liquid chromatography technique and trihydroxyindole. Briefly, catecholamines were adsorbed to 20 mg of acid-washed activated alumina from 1 ml of the plasma sample and eluted with 100 μl of 0.2 mol/l acetic acid, including EDTA and Na2S2O5. Seventy microliters of alumina-treated sample was injected onto the column (Nucleosil 5C18, 4.6×250 mm) with 0.1 mol/l sodium phosphate buffer (pH 3.1). Constant flow rate was 0.8 ml/min, and the column was operated at 40°C. To this column effluent, the following reagents for trihydroxyindole reaction were added sequentially and automatically: 0.42 ml/min of 0.5 mol/l phosphate buffer solution, 0.32 ml/min of 2.1 mmol/l potassium ferricyandate, 0.23 ml/min of 4.0 mmol/l ascorbic acid, and 0.32 ml/min of 5.0 mmol/l sodium hydroxide. The reaction was carried out in three mixing coils in the incubator at 30°C. Air bubbles were added to the column effluent and removed just before the inlet of the spectrophotometer (Hitachi F-1050; wavelength: excitation, 410 nm; emission, 510 nm). Sensitivity of this method for NE was 10 pg/ml; coefficient of variation was 7.9%.

Postural Change Test and Ambulatory Blood Pressure Monitoring

In the patients with SDS, postural change test and ambulatory blood pressure monitoring (ABPM) for 24 hours were done before and after xamoterol administration. The effects of postural change were evaluated before and 1 minute after standing up with the use of the automatic sphygmomanometer (Nihon Kohrin BP-103N) (Table 2). For ABPM, we used the noninvasive sphygmomanometer (model 5200, Spacelab). The initial ABPM was performed 2 to 3 days after the isoproterenol infusion test, and the second ABPM was done after 2 weeks of xamoterol (200 mg b.i.d., 8 AM and 6 PM). Recording intervals were every 15 minutes from 7 AM to 6 PM and every hour from 6 PM to 7 AM the following day for a total of 57 recordings. Patients were asked to perform their usual daily activities. The obtained blood pressure and heart rate values were analyzed using the averages of the whole 24-hour recording—daytime recordings (from 7 AM to 4:59 PM) and nighttime recordings (from 5 PM to 6:59 AM). Trendgrams of blood pressure and heart rate were obtained using averages calculated for each hour.

Clinical Benefits

Clinical benefit was assessed by asking the patients about symptoms of dizziness and daily activities, and the number of syncopal attacks per week was compared between pretreated week and treated second week.

Statistical Analysis

Statistical evaluation was performed using paired or nonpaired t test; probability value of less than 0.05 was considered significant.

Results

Plasma NE Concentration

Plasma NE concentration at rest was 178±83 pg/ml in normal subjects and 54±15 pg/ml in SDS patients; this was a significant difference (p<0.05). After 10-minute standing, plasma NE level elevated to 318±143 pg/ml in normal subjects (p<0.05) and was 74±24 pg/ml in SDS patients (Table 2); this was a significant difference in increasing value and rate between normal subjects and SDS patients (p<0.05).

Isoproterenol Infusion Test

Isoproterenol infusion produced a 17±7-mm Hg rise of systolic pressure in normal subjects (p<0.01) and a 25±16-mm Hg fall in SDS patients (p<0.01), a significant difference (Figure 1). Heart rate was increased by 23±8 beats per minute in normal subjects (p<0.01) and by 60±15 beats per minute in SDS patients (p<0.01). The increasing value of heart
rate in SDS patients was significantly greater than that of normal subjects (Figure 1).

Effects of Xamoterol

Postural change test. The results of postural change testing are shown in Table 2. Xamoterol increased systolic pressure in the upright position from 74±13 to 105±24 mm Hg (p<0.05). In patients 2, 3, and 5, xamoterol also increased diastolic pressure in the upright position from 53±10 to 82±5 mm Hg (p<0.05).

Ambulatory blood pressure and heart rate monitoring. The 24-hour averaged blood pressure elevated significantly from 106±5 to 117±8 mm Hg in systole and from 69±6 to 77±8 mm Hg in diastole after xamoterol administration (Figure 2, panels a and b). The 24-hour averaged heart rate was increased significantly from 70±10 to 83±14 beats per minute (Figure 2, panel c).

During the daytime, from 7 AM to 5 PM, xamoterol produced significant increases in systolic blood pressure from 105±8 to 114±11 mm Hg and in heart rate from 71±10 to 82±13 beats per minute (Figure 3, panels a and c). Diastolic blood pressure was increased from 65±5 to 75±9 mm Hg, but this was not significant (Figure 3, panel b).

During the nighttime, from 5 PM to 7 AM of the following day, xamoterol significantly increased systolic blood pressure from 110±4 to 124±10 mm Hg, diastolic blood pressure from 71±8 to 79±7 mm Hg, and heart rate from 69±10 to 85±15 beats per minute (Figure 3, panels b and c).

During the control period, blood pressures remained at low levels throughout the morning but began to rise slowly in the afternoon and tended to fluctuate at relatively high levels at night (Figure 4). However, such tendencies were unclear in heart rate. After xamoterol administration, systolic blood pressure, diastolic blood pressure, and heart rate all
exhibited higher values than during the control period. The improvement of low blood pressure levels in the morning and the enhancement of high blood pressure levels at night were apparent.

Clinical benefits. Improvement in the symptom of dizziness was reported in four patients (Table 2); in cases 2 and 5, it was large enough to enable them to increase their daily activities.

Discussion

In this study, we observed the beneficial effects of xamoterol for the treatment of postural hypotension on SDS patients. A β-blocker, pindolol, which has some intrinsic sympathomimetic activity, has been reported to be effective on patients with postural hypotension who were suggested to have peripheral or postganglionic-type sympathetic nerve degeneration but was ineffective on patients with SDS. It is interesting that our finding that xamoterol, which has much greater intrinsic sympathomimetic activity, was effective on patients with SDS.

Xamoterol increases heart rate and systolic blood pressure in healthy subjects significantly but fails to produce any significant changes in patients with mild heart failure. These different responses can be understood in light of the fact that xamoterol acts as a β1-agonist or as a β2-antagonist, depending on the subject's prevailing sympathetic tone. For this reason, the endogenous catecholamine levels of our patients with SDS should predict the effects of xamoterol.

The plasma NE levels of SDS patients were reported to be almost even with that of normal subjects. On the other hand, Bannister and Kita indicated that the concentration was significantly lower than that of normal subjects (76 versus 550 pg/ml and 55 versus 189 pg/ml, respectively). They also reported the lack of NE increase on the upright position in SDS patients. In the present study, plasma NE was at a low of 53.8 pg/ml at rest and failed to increase on standing. Bannister considered that these observations suggested lack of NE release at sympathetic endings.

With respect to the sensitivity of SDS patients to exogenous catecholamines, great increases in heart rate and marked decreases in blood pressure in response to low concentrations of isoproterenol were reported. In our isoproterenol test, we also found marked increases in heart rate and decreases in blood pressure that were significantly greater than those in normal subjects. These results suggest a hypersensitive state in response to β1- and β2-adrenoceptor stimulants. The upregulation of lymphocyte β-adrenoceptors of patients with SDS is considered to support our suggestion.

The intrinsic sympathomimetic activity of xamoterol has been reported to be 43%, higher than the 20% of pindolol. Whereas xamoterol is devoid of any β2-adrenergic property that may produce vasodilatation, pindolol is a nonselective β-blocker with a β2-adrenoceptor agonistic property. The high β1-adrenoceptor agonistic property of xamoterol and the prevailing hypersensitive state of β1-adrenoceptors in our SDS patients probably increased cardiac output by marked increases in heart rate and stroke volume. Additionally, the lack of β2-adrenergic property in xamoterol may have also contributed to the increase in systolic pressure by maintaining vascular tone.

For diagnosing orthostatic hypotension and evaluating therapeutic efficacy, the postural change test usually has been performed. In our postural change test, we also found that blood pressure in the upright position after xamoterol administration was significantly greater than that in the control period. However, Mann demonstrated a consistent circadian trend in blood pressure of the patients with postural hypotension (with the lowest pressure in the morning and highest at night) and found a correlation of the nadir of the blood pressure measurements with the reported time of peak incidence of orthostatic symptoms. In our cases, there was a low blood pressure period in the morning. After xamoterol administration, we found a significant increase in daytime averaged value of blood pressure and improvement of orthostatic symptoms. These findings suggest that the increase in blood pressure was translated into clinical benefit, especially in the morning. However, we also observed that the increase in blood pressure was more pronounced at night. Large swings of blood pressure values in patients with postural hypotension are known to show hypertensive levels exacerbated by treatment. Therefore, our findings may suggest the availability of another optimal dosage time for xamoterol, such as once daily in the morning.

Conclusions

We have reported a beneficial effect of xamoterol to orthostatic hypotension of patients with SDS. Our data showed a significant elevation of blood pressure, with clinical improvement in four of five patients. Because SDS is such a disabling condition and because there is little to offer these patients, xamoterol may represent an important therapeutic intervention in at least some patients with this disease. Pronounced increase in blood pressure during the night may suggest another beneficial prescription for xamoterol. We hope that trial of therapy with xamoterol is justified in individual patients.

Acknowledgments

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