Blood pressure and plasma norepinephrine responses to dexfenfluramine in obese postmenopausal women

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ABSTRACT  Dexfenfluramine has been shown to reduce body weight and lower blood pressure in obese individuals. However, it is not clear whether the blood pressure–lowering effect is due to dexfenfluramine or to the loss of weight. This project was designed to study the effect of a 5-d treatment of dexfenfluramine on blood pressure changes in obese postmenopausal women. Twenty women aged 51–60 y matched for body mass index [BMI (in kg/m²) of 34.5–50.1] were assigned to either the dexfenfluramine group (15 mg orally twice a day for 5 d) or the control group. All subjects were instructed about an isoenergetic diet. Twenty-four–hour ambulatory blood pressure measurement (ABPM) technique has the advantage of providing continuous monitoring of blood pressure over a 24-h period (14). This ambulatory blood pressure measurement (ABPM) technique has the advantage of providing continuous monitoring of blood pressure over a 24-h period and eliminating the blood pressure response to stress when patients report to the study center and blood pressure measurements were performed by trained personnel who used a sphygmomanometer (11) or random-zero sphygmomanometer (13) after the subjects had rested in a sitting or supine position. This technique may not be sensitive enough to detect blood pressure changes in subjects during the entire study period. With the recent development of compact pumps it is now possible to record a subject’s blood pressure over a 24-h period (14). This ambulatory blood pressure measurement (ABPM) technique has the advantage of providing continuous monitoring of blood pressure over a 24-h period and eliminating the blood pressure response to stress when patients come to a research center.

This study was designed to examine the effects of a 5-d treatment of dexfenfluramine on changes in blood pressure in obese postmenopausal women consuming an isoenergetic diet by using both the new ABPM technique and the conventional method. We also examined the effects of dexfenfluramine on circulating concentrations of catecholamines, glucose, insulin, and lipids.

SUBJECTS AND METHODS

Obese postmenopausal women with body mass indexes (BMIs; kg/m²) ≥30 and ≤55 were recruited from the outpatient medicine department of the University Hospital of Ulm. Subjects were excluded if they 1) had obesity of endocrine origin, 2) acute or chronic disease or a psychiatric disorder, 3) were receiving comitant loss of body weight, or to changes in food intake while patients are taking the medication (10). Recently, it was shown that short-term treatment with dexfenfluramine caused a reduction in serum norepinephrine concentration and blood pressure when subjects maintained a constant daily energy intake and body weight (11, 12). One of the major concerns about the previous studies is the technique with which the blood pressure recordings were obtained. In the past, subjects were asked to report to the study center and blood pressure measurements were performed by trained personnel who used a sphygmomanometer (11) or random-zero sphygmomanometer (13) after the subjects had rested in a sitting or supine position. This technique may not be sensitive enough to detect blood pressure changes in subjects during the entire study period. With the recent development of compact pumps it is now possible to record a subject’s blood pressure over a 24-h period (14). This ambulatory blood pressure measurement (ABPM) technique has the advantage of providing continuous monitoring of blood pressure over a 24-h period and eliminating the blood pressure response to stress when patients come to a research center.

This study was designed to examine the effects of a 5-d treatment of dexfenfluramine on changes in blood pressure in obese postmenopausal women consuming an isoenergetic diet by using both the new ABPM technique and the conventional method. We also examined the effects of dexfenfluramine on circulating concentrations of catecholamines, glucose, insulin, and lipids.

INTRODUCTION

The serotoninergic agent dexfenfluramine, a dextrorotatory stereoisomer of fenfluramine, was shown recently to be effective in the treatment of obesity (1). Dexfenfluramine inhibits serotonin reuptake into presynaptic nerve endings and stimulates serotonin release into the synaptic cleft (2, 3); this has been shown to be capable of reducing food intake and sweet cravings in humans (4, 5). In addition to its anorectic activity, dexfenfluramine also reduces blood pressure in normotensive obese patients (6, 7), as well as in hypertensive obese patients (8, 9). However, it has been difficult to determine whether the reduction in blood pressure is due primarily to dexfenfluramine, to the con-
hormone replacement therapy, 4) were habituated to drugs or alcohol, 5) were smokers, or 6) were unable or unwilling to comply with the protocol requirements. Subjects gave written informed consent to the protocol, which was approved by the Institutional Review Board of University of Ulm.

Heights of subjects without shoes were measured with a wall-mounted stadiometer to the nearest 0.5 cm and body weight was measured with a scale to the nearest 0.1 kg. Waist and hip circumferences were measured to the nearest 0.5 cm with a measuring tape. Lean body mass and fat mass were measured by near infrared interactance at the anterior biceps margins by using the Futrex-5000i body composition meter (Futrex Inc, Gaithersburg, MD).

Insulin was measured by radioimmunoassay (RIA-gnost Insulin; Behring-Werke AG, Marburg, Germany). Blood glucose was measured by using an enzymatic ultraviolet test kit (Boehringer Mannheim, Mannheim, Germany). Triacylglycerol was measured by using an enzymatic colorimetric test kit and total cholesterol was measured by using an enzymatic kit based on the CHOD-PAP method (Boehringer Mannheim). HDL cholesterol was measured in the supernate after precipitation of VLDL and LDL with phosphotungstic acid and magnesium. LDL cholesterol was calculated by using the Friedewald equation (15).

Blood pressures were obtained conventionally by the same researcher using a standard mercury column sphygmomanometer. All patients were instructed to rest in the supine position for 15 min before measurement of blood pressure. All conventional blood pressure measurements were obtained between 0800 and 0900.

ABPM for 24 h was performed with the Tenso24 apparatus (Speidel & Keller, Junghingen, Germany), which was programmed to obtain blood pressure and heart rate readings at 15-min intervals during the day (0700–2300) and at 30-min intervals during the night (2330–0630). Specific cuffs (Speidel & Keller) were selected, which have appropriate sizes for patients with various degrees of obesity. Calibration accuracy was checked before actual testing by connecting the Tenso24 to a mercury column to check that pressures throughout the range were within 4 mm Hg. The pre- and posttreatment ABPMs were performed on weekdays for each subject. Subjects were asked to maintain their routine activities but to avoid exercise during the study period. They were instructed to keep the arm with the cuff immobile at the time of each cuff inflation.

Diet

All subjects were instructed on a standardized diet by a nutritionist to maintain their body weight within 1 kg for 4 wk before starting the study. The energy requirement was estimated based on individual total energy needs (in MJ/d) by using the following formula derived by Owen et al (16):

\[
\text{Basal energy needs} = \text{resting metabolic rate} \times \text{activity factor (1)}
\]

where resting metabolic rate for women is 3.34 + (0.03 \times \text{body wt, in kg}), and activity factors are 1.2 for low levels of activity and 1.4 for moderate activity.

Study design

Twenty-four postmenopausal women whose body weight had been stable for 4 wk were selected to enter the study. Subjects with similar BMIs (ranging from 34.5 to 50.1) were paired and randomly assigned to either the dexfenfluramine or the control group.

The dexfenfluramine group were instructed to take 15 mg dexfenfluramine twice a day at 0800 and 2000 for 5 d. The weight, height, ABPM, and circulating concentrations of catecholamines, glucose, insulin, and lipids were measured before and were repeated at the end of the study. One subject in the control group was dropped from the study because weight loss during the 5 d was excessive (>1.5 kg). One subject in the dexfenfluramine group was dropped because she was not able to visit the hospital on the fifth day after starting the treatment. Data on 20 women (10 paired subjects) who finished the study were analyzed.

Statistical analysis

Data were analyzed by using the BMDP program (BMDP Statistics Software, Los Angeles). Results are expressed as means ± SD. Differences in categorical variables between the two study groups were assessed with \( t \) tests with a Bonferroni correction. When subjects were divided into groups (control or dexfenfluramine), comparisons of blood pressure and heart rate were made by three-way analysis of variance (ANOVA) with repeated measures with one group factor and two within-subject factors for method and time. Because three tests were performed with the same sample, significant levels of probability were adjusted according to Bonferroni and \( P \) values < 0.0166 were considered statistically significant at the 5% level. Assessment of treatment effects on metabolic variables and on blood pressure and heart rate over 24 h were made by two-way ANOVA for repeated measures with one between-subjects factor for group and one within-subject factor for time. A contrast analysis was applied to determine differences between day and night. \( P \) values < 0.05 were regarded as indicating statistical significance.

RESULTS

The characteristics of the 10 pairs of obese postmenopausal women are shown in Table 1. The two groups were matched for age, BMI, body composition (lean mass and fat mass), and waist-to-hip ratio. There were no weight changes during the study period.

Blood pressure and heart rate measurements in the two groups at the beginning and the end of the study by both the conventional and ABPM methods are shown in Table 2. In the control group, no changes in systolic blood pressure, diastolic blood pressure, or heart rate were observed during the study by using either the conventional or the ABPM method. However, note that the systolic blood pressures obtained by ABPM in the control

| TABLE 1 |
| Baseline characteristics of subjects |
| Control group (n = 10) | Dexfenfluramine group (n = 10) |
| Age (y) | 54.5 ± 3.2 | 55.4 ± 4.3 |
| Body weight (kg) | 105.7 ± 24.6 | 106.8 ± 19.4 |
| Height (m) | 1.63 ± 0.07 | 1.64 ± 0.10 |
| Body mass index (kg/m²) | 39.3 ± 5.8 | 38.4 ± 6.3 |
| Body fat (kg) | 46.6 ± 15.7 | 47.6 ± 14.3 |
| Lean body mass (kg) | 59.5 ± 14.3 | 58.6 ± 12.8 |
| Waist (cm) | 108.0 ± 12.2 | 110 ± 13.8 |
| Hip (cm) | 129.5 ± 12.2 | 130.8 ± 10.7 |
| Waist-to-Hip ratio | 0.83 ± 0.05 | 0.84 ± 0.04 |

\( \bar{x} \pm SD \).
group were significantly lower than those obtained by the conventional method. By the conventional method, subjects in the dexfenfluramine-treated group also did not show any significant change in systolic blood pressure, diastolic blood pressure, or heart rate before and at the end of the study. However, by using ABPM, systolic and diastolic blood pressures were reduced after 5 d of treatment with dexfenfluramine.

Systolic blood pressure measurements over 24-h in the two groups are shown in Figure 1. ANOVA showed that subjects in the dexfenfluramine group had lower systolic blood pressures than those in the control group ($P < 0.001$). In both the control and treatment groups, the daytime systolic blood pressure measurements were significantly higher than the nighttime measurements ($P < 0.001$). Furthermore, when the daytime and nighttime systolic blood pressure measurements were analyzed individually, the dexfenfluramine group had significantly lower systolic blood pressures only in the daytime ($P < 0.001$). The diastolic blood pressure measurements using ABPM in the control and dexfenfluramine groups are shown in Figure 2. Again, the diastolic blood pressures of subjects in the dexfenfluramine group were lower than those of the control group, and daytime diastolic blood pressure measurements were significantly higher than the nighttime measurements in both groups ($P < 0.001$). The dexfenfluramine-treated subjects had reduced heart rate only during the daytime when compared with the control group ($P < 0.001$; Figure 3).

Serum concentrations of norepinephrine, epinephrine, glucose, insulin, triacylglycerol, total cholesterol, LDL, and HDL at baseline and day 5 in the control and dexfenfluramine-treated groups are shown in Table 3. There was a significant reduction in norepinephrine concentration at day 5 when compared with baseline within the dexfenfluramine-treated group ($P < 0.05$). The norepinephrine concentration at day 5 in the dexfenfluramine-treated group was also significantly lower than that of the control group ($P < 0.05$). No significant differences were shown in the circulating concentrations of epinephrine, glucose, insulin, triacylglycerol, cholesterol, HDL, or LDL at baseline and after 5 d of treatment both within the control and dexfenfluramine groups and between the control and dexfenfluramine groups.

### Table 2

<table>
<thead>
<tr>
<th></th>
<th>Control group</th>
<th>Dexfenfluramine group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1</td>
<td>Day 5</td>
</tr>
<tr>
<td>Conventional blood pressure measurement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>146 ± 15</td>
<td>144 ± 12</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>88 ± 10</td>
<td>86 ± 9</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>82 ± 14</td>
<td>81 ± 9</td>
</tr>
<tr>
<td>Ambulatory blood pressure measurement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>127 ± 10</td>
<td>124 ± 12</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>80 ± 11</td>
<td>76 ± 10</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>82 ± 10</td>
<td>83 ± 11</td>
</tr>
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</table>

$\bar{x} \pm$ SD. Significant effect of method for SBP ($P = 0.0000$) and DBP ($P = 0.0051$). Significant effect of time for SBP ($P = 0.0007$) and DBP ($P = 0.0000$). Significant interaction of group and time for SBP ($P = 0.0147$) and DBP ($P = 0.0062$). All by three-way repeated-measures ANOVA.
DISCUSSION

In this study, we showed that a 5-d treatment with dexfenfluramine significantly reduced blood pressure and heart rate in obese postmenopausal women. Because all subjects maintained their body weight throughout the study, the reduction in blood pressure and heart rate was likely the result of direct pharmacologic action of dexfenfluramine. Several previous studies examined the association between dexfenfluramine treatment and blood pressure changes but found inconsistent results (6, 7, 17, 18). This inconsistency could be explained by the following reasons. First, weight loss associated with taking dexfenfluramine was not carefully controlled in these studies. Second, conventional blood pressure measurements were used in previous studies and have been characterized by high variability; measurements of individual blood pressures in the morning alone may not be able to detect small differences in blood pressure. In this study, we used 24-h noninvasive blood pressure monitoring under ambulatory conditions, and this allowed the recording of blood pressure variations during the day and night. We showed that the blood pressure measurements obtained by ABPM were lower than those obtained by the conventional method in both groups. This could be explained by the fact that ABPM gave an average daily blood pressure, which takes into account the lower nighttime blood pressure in all subjects.

We showed that a 5-d treatment with dexfenfluramine resulted in a significant decrease of plasma norepinephrine concentrations. This agrees with the results of two earlier reports (11, 12). Although plasma norepinephrine concentrations in the circulation may not be a sensitive index for activity of the sympathetic nervous system (19), the norepinephrine concentrations in the dexfenfluramine-treated group were 33.8% lower than those in the control group. This suggests that dexfenfluramine may inhibit sympathetic nervous system activity. Although it has been shown that an energy-restricted diet may induce a decrease in sympathetic nervous system activity (20, 21), energy intake in the control group was the same as in the dexfenfluramine group in our study.

There are contradictory findings about sympathetic nervous system activity in obesity. Several reports show that obese patients have increased sympathetic nervous system activity as reflected by urin ary norepinephrine excretion (22, 23) and plasma norepinephrine concentrations (24–26). Other reports have not found a relation between obesity and sympathetic nervous system activity (21, 27, 28). Alternatively, some investigators have found an inverse association of sympathetic activity and obesity (29–31). Lack of a conclusive relation between sympathetic activity and obesity may be due partly to the various clinical subtypes of obesity. Such subtypes include patients in whom obesity is an important health risk and in whom hypertension develops. In the Normative Aging Study, a direct correlation between central obesity, blood pressure, and norepinephrine concentrations was shown (23). In central obesity, sympathetic activity may contribute to increases in blood pressure through sympathetic stimulation of the vasculature. In our study, norepinephrine concentrations and blood pressure in normotensive obese women with the peripheral type of obesity decreased during dexfenfluramine treatment. It is not known whether patients with central obesity would also benefit from treatment with dexfenfluramine, particularly to inhibit sympathetic nervous system activity and to prevent development of hypertension.

In conclusion, our results show that dexfenfluramine treatment in obese postmenopausal women reduced blood pressure, heart rate, and plasma norepinephrine. The effects were observed without energy restriction and without weight loss, suggesting a direct hypotensive effect of the drug. Treatment with dexfenfluramine may be of particular value in obese patients with high sympathetic nervous system activity and hypertension.

TABLE 3
Metabolic variables in obese women during a weight-maintenance diet

<table>
<thead>
<tr>
<th>Metabolic Variable</th>
<th>Control group</th>
<th>Dexfenfluramine group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Day 5</td>
</tr>
<tr>
<td>Norepinephrine (nmol/L)</td>
<td>2.52 ± 0.7</td>
<td>2.41 ± 0.5</td>
</tr>
<tr>
<td>Epinephrine (nmol/L)</td>
<td>229 ± 98</td>
<td>245 ± 125</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>5.4 ± 1.0</td>
<td>5.3 ± 0.7</td>
</tr>
<tr>
<td>Insulin (pmol/L)</td>
<td>222 ± 114</td>
<td>200 ± 136</td>
</tr>
<tr>
<td>Triacylglycerol (mmol/L)</td>
<td>2.16 ± 1.9</td>
<td>2.40 ± 1.5</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>5.55 ± 0.9</td>
<td>5.63 ± 0.9</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>3.21 ± 0.9</td>
<td>3.25 ± 1.1</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.36 ± 0.4</td>
<td>1.29 ± 0.3</td>
</tr>
</tbody>
</table>

*P < 0.001. Significant effect of time for norepinephrine, P = 0.0000. Significant interaction of group and time for norepinephrine, P = 0.0003. Both by two-way repeated-measures ANOVA.*
REMARKS

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