Absence of Cardiac Valve Dysfunction in Obese Patients Treated with Sibutramine

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Abstract

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Objective: Serotonin-releasing agents prescribed as weight-loss medications have been implicated as a cause of acquired aortic and mitral valve abnormalities. Sibutramine hydrochloride (MERIDIA®) is a serotonin and norepinephrine reuptake inhibitor with proven efficacy of weight reduction. The purpose of this study was to determine the incidence of cardiac valve disease in sibutramine-treated patients.

Research Methods and Procedures: Obese patients with type 2 diabetes mellitus enrolled in an ongoing double-blind, placebo-controlled, parallel-arm, 12-month study of sibutramine (followed by a 12-month open label extension) underwent transthoracic echocardiographic imaging and color Doppler interrogation for assessment of cardiac valve anatomy and function.

Results: A total of 210 patients were evaluated. Of these, 133 were receiving sibutramine (72 in the double-blind period), and 77 were receiving placebo. The mean ± Standard Deviation age was 54±9 years, and the mean duration of treatment was 229±117 days (approximately 7.6 months). The prevalence of left-sided cardiac valve dysfunction was low and similar for the two treatment groups (sibutramine 3/133, or 2.3%; placebo 2/77, or 2.6%). All five cases were cases of aortic insufficiency; four were mild, one was severe (in a placebo patient). All three sibutramine cases were patients over age 50; two had a history of systemic hypertension.

Conclusion: The prevalence of left-sided cardiac valve dysfunction was not higher than background in obese patients treated with sibutramine for an average of 7.6 months.

Key words: anti-obesity drugs, heart valves, echocardiography, mitral valve insufficiency, aortic valve insufficiency

Introduction

Serotonin-releasing agents prescribed as weight-loss medications recently have been implicated as a cause of acquired aortic and mitral valve abnormalities. The initial report identified valve abnormalities among patients receiving combination therapy with fenfluramine and phentermine (1). Subsequently, echocardiographic evidence of valve dysfunction was found among 92 (31.6%) of 291 asymptomatic patients treated at five centers with either dexfenfluramine or fenfluramine with or without phentermine (2). These findings prompted voluntary withdrawal of dexfenfluramine and fenfluramine in the United States and subsequently from the worldwide market. More recently, two larger studies have confirmed an excess prevalence of mitral and aortic valve pathology among patients exposed to fenfluramine, either with or without phentermine (3,4). A large-scale surveillance study has recently suggested no increase in valvular heart disease among patients treated with dexfenfluramine alone (5). The mechanism of acquired left-sided valve abnormalities associated with fenfluramine and dexfenfluramine has not been determined, but both fenfluramine and dexfenfluramine are serotonin-releasing agents. The valvular abnormalities that have been seen are morphologically similar to those noted in patients with the carcinoid syndrome.

Sibutramine (MERIDIA®; Knoll Pharmaceutical Co.,

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Mt. Olive, NJ), an arylbutylcycloalkylamine, is a serotonin and norepinephrine reuptake inhibitor with demonstrated efficacy in weight management. Sibutramine has been approved recently for use in the United States as a weight-control medication. Although it has a mechanism of action distinct from that of the serotonin-releasing agents fenfluramine and dexfenfluramine, it does act on the serotonin system. The effect of sibutramine on cardiac valvular anatomy and function has not been reported previously. Similarly, the effects of other reuptake inhibitors that act on serotonin (e.g., fluoxetine, venlafaxine, sertraline, imipramine, amitriptyline) on cardiac valvular anatomy and function have not been reported.

The incidence of significant left-sided valvular heart disease in a population of asymptomatic subjects is known to be low. However, robust data are currently available only in a general population of relatively young age (6). The incidence of valvular heart disease is known to be higher among patients who are older or who have systemic hypertension (7–10). The incidence of echocardiographically detectable valvular heart disease in a population of middle-aged obese patients, representative of patients in whom valve disease was observed in association with fenfluramine and dexfenfluramine therapy has only recently been described (4,5).

The purpose of the present study was twofold. First, we sought to evaluate the incidence of significant echocardiographically detectable left-sided valvular heart disease in a group of obese patients referred for but not treated with weight-loss drugs. Second, we sought to evaluate the prevalence of echocardiographically detectable left-sided valve abnormalities among patients treated with sibutramine.

Methods

Patients and Study Design

Eligible patients, all of whom were currently enrolled in an ongoing multicenter study of sibutramine, were evaluated with transthoracic echocardiography and Doppler interrogation of all four cardiac valves. The ongoing study was a randomized, double-blind, placebo-controlled, parallel-arm, 12-month study followed by 12 months of open label therapy in obese patients with type 2 diabetes mellitus who had not received antidiabetic medication previously. All patients were between 25 and 70 years of age and had a body mass index (BMI, weight/height^2)$\geq$28 kg/m^2 (obesity threshold = 27 kg/m^2) at the start of the ongoing study. Patients were excluded from participation in the echocardiography study if they had known preexisting documented valvular heart disease (except for non-clinically significant mitral valve prolapse) prior to initiation of the ongoing weight-loss study or if they had used centrally active prescription weight-control medications for more than 1 week within the previous 5 years. Patients in the double-blind phase were receiving either sibutramine 15 mg or placebo daily. Patients in the open treatment phase were receiving sibutramine 15 mg daily, although the dose could be increased to 20 mg if they gained weight on 15 mg. All patients provided written informed consent and the protocol was approved by the ethical committees at the participating centers.

Echocardiography

All patients in the above noted ongoing sibutramine study were contacted to undergo echocardiographic screening while still enrolled in the study and while still on study medication (placebo or sibutramine). Each patient underwent transthoracic two-dimensional echocardiography and color Doppler examination with specific attention to the presence or absence of valvular abnormalities. Transthoracic echocardiography was performed using current generation two-dimensional echocardiographic scanners. Instrumentation provided two-dimensional images at $\geq$75° sector, at $\geq$30 Hz frame rate with $\geq$128 grey scale shades and color flow imaging at frame rates $\geq$14 Hz. Transducer frequency varied from 2 to 5 MHz depending on the available imaging windows. Standard echocardiographic views were recorded on videotape and transferred to a central laboratory for interpretation.

Left ventricular internal short axis dimensions, wall thickness, and left atrial dimensions were all measured from the parasternal long axis view directly from the two-dimensional image. The left ventricular internal dimension was measured in diastole, as timed from the R-wave, and in systole, as the smallest internal dimension at the level of the mitral valve chordae. The left atrial dimension was measured in systole.

For both the aortic and mitral valves, an anatomic assessment was made of valvular morphology, which included categorization as either normal, showing mild degrees of age-related fibrosis, showing a pathologic degree of either focal or diffuse thickening and fibrosis, or showing a distinct mass. Additionally, valves were categorized with respect to obvious identifiable pre-existing structural lesions such as typical rheumatic heart disease with mitral stenosis, bicuspid aortic valve, etc.

Aortic insufficiency was categorized as absent, minimal (within normal limits), mild, moderate, or severe using a combination of qualitative and quantitative parameters. For aortic insufficiency, qualitative parameters included depth of penetration into the left ventricular outflow tract as well as overall jet area, density of the spectral profile signal, and presence of reversal of flow in the descending thoracic aorta. Quantitative parameters included pressure half time of aortic insufficiency jet deceleration and assessment of the aortic insufficiency jet height, indexed to left ventricular outflow tract dimension. For the latter, minimal aortic insufficiency was considered consistent with a jet height to outflow tract height ratio <5%, mild 5% to 20%, moderate 21% to 59% and severe >60%.

Mitral insufficiency was evaluated qualitatively and quantitatively as absent, minimal, mild, moderate, or severe. Minimal mitral regurgitation was considered present when there was an incompletely developed jet that was not holosystolic, was less than 2- to 3-mm in diameter at its origin and which penetrated less than 15 mm into the left atrium. Mild mitral insufficiency was considered present when there was a completely developed jet present throughout systole which encompassed <20% of the left atrial area. Mitral insufficiency was considered moderate for jets which encompassed 20% to 40% of the left atrial area and severe when >40% of the area was encompassed.

Left-sided valve regurgitation was assumed to be of potential clinical significance based on the findings of previously reported literature and at thresholds established for "case definition" by the United States Food and Drug Administration (2). In brief, mitral regurgitation was taken to be of potential clinical significance if greater than mild in severity, and aortic regurgitation if greater than minimal.

Right-sided valvular lesions were evaluated on a qualitative basis. Both the pulmonic and tricuspid valve were assessed for degrees of valvular thickening, prolapse, mass or other anatomic abnormalities. Pulmonic insufficiency was graded in a manner identical to that for aortic insufficiency. Tricuspid insufficiency was graded in a manner identical to that for mitral insufficiency. Additionally, when tricuspid insufficiency was present, the spectral profile of the tricuspid regurgitation jet was used to estimate the right ventricular-right atrial pressure gradient.

All echocardiograms were read by one of two experienced echocardiographers (DSB or WFA) blinded to status or duration of drug therapy. A second independent blinded reading for aortic and mitral pathology was performed on 25% of studies. Any descrepancies were resolved by consensus.

Statistical Analysis

The treatment groups were classified as follows: 1) Patients randomized to sibutramine were included in the analysis as sibutramine patients; 2) Patients randomized to placebo who had echocardiography performed while receiving placebo were classified as placebo patients; and 3) Patients randomized to placebo who had echocardiography performed while receiving sibutramine in the open-treatment phase were classified as sibutramine patients.

For ordinal categorical data, the Cochran–Mantel–Haenszel (CMH) procedure (11,12) was used to generate an overall comparison between the treatment groups. For binary data, point estimates and 90% confidence intervals were computed for the treatment proportions, for the difference in treatment proportions and for the odds ratio. All computations were performed using the FREQ procedure in SAS® (version 6.12) (13).

Table 1. Baseline characteristics

	Treatment group			
Parameter	**Sibutramine (n=133)**	**Sibutramine double-blind* (n=72)**	**Placebo (n=77)**	**Overall (n=210)**
Male [n (%)]	52 (39.1)	35 (48.6)	34 (44.2)	86 (41.0)
Female [n (%)]	81 (60.9)	37 (51.4)	43 (55.8)	124 (59.0)
Age (mean ± S years)†	54.0±9 (range 25–71)	53.2±9 (range 25–68)	54.8±8 (range 35–71)	54.3±9 (range 25–71)
Age <50 years [n (%)]	36 (27.1)	21 (29.2)	24 (31.2)	60 (28.6)
Age ≥50 years [n (%)]	97 (72.9)	51 (70.8)	53 (68.8)	150 (71.4)
Duration of Treatment (mean ± S days)	229±134 (range 14–487)	227±82 (range 79–375)	228±79 (range 86–379)	229±117 (range 14–487)
Duration of Treatment <180 days [n (%)]	56 (42.1)	25 (34.7)	23 (29.9)	79 (37.6)
Duration of Treatment ≥180 days [n (%)]	77 (57.9)	47 (65.3)	54 (70.1)	131 (62.4)
History of Hypertension [n (%)]	58 (43.6)	29 (40.3)	37 (48.1)	95 (45.2)

*Patients in the double-blind phase at the time of echocardiography; this group is a subset of the sibutramine group.
†S, standard deviation.

Results

Study Patients

Two hundred and thirty-seven patients were enrolled in the initial double-blind, placebo-controlled study of weight loss in diabetic patients. Of these, 25 (10.5%) discontinued participation prior to performance of echocardiography, 20 due to adverse events (none of which were consistent with cardiac valve disease) and 5 for other reasons. Of the 212 patients remaining, one was excluded from participation because of a history of aortic valve disease that predated entry into the weight-loss study, and another underwent echocardiography but was excluded from the analysis because an abnormal echocardiogram indicating aortic and mitral valve disease that predated entry into the weight-loss study was discovered. All of the remaining 210 patients participated in the echocardiography study, and all (100%) underwent echocardiographic imaging and analysis.

Of the 210 patients analyzed, 149 were in the double-blind treatment phase, with 72 receiving sibutramine and 77 receiving placebo. The remaining 61 patients were in the open treatment phase at the time of echocardiography. Patients in the study had received sibutramine or placebo for 7.6±3.9 months (Table 1). Baseline characteristics were comparable for the treatment groups (Table 1). The majority of the patients were over the age of 50 (71%) and female (59%). Almost half (45%) of the patients had a history of hypertension.

Echocardiographic Imaging

There were no significant differences between treatment groups in any echocardiographic parameter. A total of 54 (25.7%) of the 210 echocardiograms underwent both primary and secondary review. There was a single (1 of 54, or 1.9%) discrepancy between readers for analysis of left-sided cardiac valvular dysfunction, in which aortic regurgitation was graded as mild by one observer and minimal by the second. Agreement was therefore 53 of 54 (98.1%) echocardiograms and 107 of 108 (99.1%) left-sided valves.

The prevalence of echocardiographic valve thickening for all valves is shown in Table 2. There were no significant differences in the prevalence of valve thickening between treatment groups. The incidence of Doppler evidence of valve regurgitation is shown in Table 3. The rates of valve regurgitation were low and similar for both treatment groups. The prevalence, 90% confidence intervals and odds ratio for left-sided valve dysfunction are shown in Table 4. The 90% confidence interval for the difference between sibutramine and placebo was narrow and included zero well within the interval. Similar results were obtained when pa-

Table 2. Echocardiographic valve thickening by treatment group [number (%)].

	n	Normal†	Thickened	Thickened‡ (focal)	Thickened‡ (diffuse)	Not Evaluable	*p*-value vs. Placebo
Aortic							
Sibutramine (all)	133	118 (88.7)	15 (11.3)	14 (10.5)	1 (0.8)		0.83
Sibutramine (double-blind)*	72	62 (86.1)	10 (13.9)	9 (12.5)	1 (1.4)		0.71
Placebo	77	70 (90.9)	7 (9.1)	6 (7.8)	1 (1.3)		
Mitral							
Sibutramine (all)	133	114 (85.7)	19 (14.3)	18 (13.5)	1 (0.8)		0.47
Sibutramine (double-blind)*	72	60 (83.3)	12 (16.7)	12 (16.7)	0		0.24
Placebo	77	67 (87.0)	10 (13.0)	8 (10.4)	2 (2.6)		
Pulmonic							
Sibutramine (all)	133	130 (97.7)	1 (0.8)			2 (1.5)	1.00
Sibutramine (double-blind)*	72	71 (98.6)	1 (1.4)			0	0.49
Placebo	77	75 (97.4)	0			2 (2.6)	
Tricuspid							
Sibutramine (all)	133	132 (99.2)	1 (0.8)			0	1.00
Sibutramine (double-blind*)	72	71 (98.6)	1 (1.4)			0	0.49
Placebo	77	76 (98.7)	0			1 (1.3)	

*Patients in the double-blind treatment phase at the time of echocardiography; this group is a subset of the sibutramine group.
†Includes normal and age-normal.
‡Subsets of "Thickened."

Table 3. Doppler evidence of valve regurgitation by treatment group [Number (%)]

Valvular abnormality / Treatment group	n	Severity of valvular regurgitation: None	Minimal	Mild	Moderate	Severe	Not evaluable	*p*-value vs. Placebo
Aortic insufficiency								
Sibutramine (all)	133	124 (93.2)	6 (4.5)	3 (2.3)	0	0	0	.64
Sibutramine (double-blind)*	72	68 (94.4)	3 (4.2)	1 (1.4)	0	0	0	.51
Placebo	77	73 (94.8)	2 (2.6)	1 (1.3)	0	1 (1.3)	0	
Mitral regurgitation								
Sibutramine (all)	133	115 (86.5)	17 (12.8)	1 (0.8)	0	0	0	.12
Sibutramine (double-blind)*	72	63 (87.5)	9 (12.5)	0	0	0	0	.25
Placebo	77	73 (94.8)	3 (3.9)	1 (1.3)	0	0	0	
Pulmonic insufficiency								
Sibutramine (all)	133	108 (81.2)	14 (10.5)	3 (2.3)	0	0	8 (6.0)	.63
Sibutramine (double-blind)*	72	59 (81.9)	8 (11.1)	2 (2.8)	0	0	3 (4.2)	.80
Placebo	77	61 (79.2)	8 (10.4)	1 (1.3)	1 (1.3)	0	6 (7.8)	
Tricuspid regurgitation								
Sibutramine (all)	133	89 (66.9)	32 (24.1)	4 (3.0)	0	0	8 (6.0)	.71
Sibutramine (double-blind)*	72	47 (65.3)	17 (23.6)	2 (2.8)	0	0	6 (8.3)	.80
Placebo	77	51 (66.2)	19 (24.7)	1 (1.3)	0	0	6 (7.8)	

*Patients in the double-blind treatment phase at the time of echocardiography; this group is a subset of the sibutramine group.

tients treated for less than 180 days were excluded from the analysis (Table 5), and when only patients in the double-blind treatment phase of the study were included in the analysis (Table 6).

Pertinent data for the five patients with echocardiographic evidence of left-sided cardiac valve dysfunction are summarized in Table 7. The mean duration of treatment for the three sibutramine-treated patients (7.2±6.2 months) was similar to that of the sibutramine group as a whole (7.6±4.5 months). All three patients were over age 50 and two had a history of systemic hypertension. One patient had been receiving sibutramine for only 3 weeks (following treatment with placebo for 1 year). The only hemodynamically significant lesion occurred in a placebo-treated patient found to have severe aortic insufficiency.

Table 4. 90% confidence intervals (CI) and odds ratio for incidence of left-sided valve dysfunction*

Treatment group	Incidence of valvular disease	90% CI
Sibutramine (n = 133)	2.3%	(0.001, 0.044)
Placebo (n = 77)	2.6%	(0.000, 0.056)
Sibutramine–Placebo	−0.3%	(−0.040, 0.033)
Odds ratio (sibutramine vs. placebo)	0.865	(0.189, 3.968)

*Severity of mild or greater aortic insufficiency and/or moderate or greater mitral regurgitation.

Table 5. 90% confidence intervals (CI) and odds ratio for incidence of left-sided valve dysfunction*: Duration of treatment ≥180 days

Treatment group	Incidence of valvular disease	90% CI
Sibutramine (n = 77)	2.6%	(0.000, 0.056)
Placebo (n = 54)	3.7%	(0.000, 0.079)
Sibutramine–Placebo	−1.1%	(−0.063, 0.041)
Odds ratio (sibutramine vs. placebo)	0.693	(0.131, 3.681)

*Severity of mild or greater aortic insufficiency and/or moderate or greater mitral regurgitation.

Table 6. 90% confidence intervals (CI) and odds ratio for incidence of left-sided valve dysfunction*: Double-blind portion of Study

Treatment group	Incidence of valvular disease	90% CI
Sibutramine (n = 72)	1.4%	(0.000, 0.037)
Placebo (n = 77)	2.6%	(0.000, 0.056)
Sibutramine–Placebo	−1.2%	(−0.050, 0.025)
Odds ratio (sibutramine vs. placebo)	0.528	(0.071, 3.931)

*Severity of mild or greater aortic insufficiency and/or moderate or greater mitral regurgitation.

Discussion

Background Prevalence of Valve Disease

Available literature has addressed the prevalence of valvular heart disease among a young, normal population and among older patients with and without systemic hypertension (6–12,14,15). The prevalence of significant valvular heart disease among middle-aged obese patients, representative of those referred for weight loss therapy, has been noted recently to range from 1.3% (4) to 4.5% (5). In the study reported here, the prevalence of significant valvular regurgitation (FDA definition) was 2.6%. Although previous reports have indicated a high prevalence of significant valvular heart disease among patients treated with fenfluramine or dexfenfluramine (2), these were observational studies without placebo control. In this regard, the high observed prevalence of valvular heart disease could have been intrinsic to the population studied rather than a result of therapy with serotonin-releasing agents.

In the present study, 77 patients referred for weight-loss therapy but treated with placebo underwent echocardiographic assessment. The demographics of the group reflected a mean age of 55 years, body mass index of >28 kg/m^2 and a 48% incidence of systemic hypertension. Among this group, there was a low prevalence of significant left- or right-sided valvular heart disease. Based on these findings, obesity does not appear to be associated with an increased incidence of significant valvular heart disease. Therefore, the high observed incidence of cardiac valve dysfunction associated with fenfluramine or dexfenfluramine therapy cannot be accounted for by the specific population studied.

Sibutramine and Valvular Function

Fenfluramine and dexfenfluramine are serotonin-releasing agents. Although sibutramine is a serotonin and norepinephrine reuptake inhibitor and therefore has a different mechanism of action, it likewise acts on the serotonin system (16). The present study demonstrates that there is a low prevalence of significant valvular heart disease associated with sibutramine therapy, which is equivalent to that observed among an appropriate control population. Our study suggests that serotonin-releasing agents and reuptake inhibitors may have disparate effects on heart valve morphology and function. Whether this is related to differential effects on extracellular serotonin levels is unknown. Neither the study reported here, nor previous studies of other weight-loss agents have evaluated actual blood serotonin levels.

Study Limitations

The average duration of therapy with sibutramine was 7.6±4.5 months. Of note, cardiac valve dysfunction associated with fenfluramine and dexfenfluramine therapy was clearly evident among patients treated for 6 months (2). More recent studies confirm the development of valvular heart disease in patients treated with fenfluramine for as little as 4 months and also suggest a higher prevalence in patients treated for longer periods (3). In the present study, selecting for only patients treated with sibutramine for ≥180 days did not suggest any increase in the incidence of valvular heart disease, suggesting that duration of therapy was not a significant limitation. However, a very late effect of sibutramine on valvular anatomy or function cannot be excluded by the present study.

The background prevalence of significant left-sided cardiac valve dysfunction among the placebo control group in the present study was 2.6%, which is slightly higher than that observed in the CARDIA study (6) of 4352 normal subjects. However, the CARDIA study included only subjects between 23 and 35 years of age. Available data suggest that the prevalence of valvular heart disease among a normal population increases with age (7–10) and with a history of systemic hypertension (9). The greater age and a high prevalence of systemic hypertension likely account for the somewhat higher observed incidence of valvular heart disease among the control population in the present study.

Finally, approximately 7% of right-sided valves in this study could not be adequately imaged for accurate analysis of regurgitation. This is likely related to body habitus in the study's population of obese patients. However, all left-sided valves could be adequately imaged in all patients.

Conclusions

In summary, the prevalence of left-sided valvular heart disease among patients treated with sibutramine was low and comparable to that observed among an appropriate placebo control group. Thus, sibutramine does not appear to be a cause of valvular heart disease. As a serotonin and norepinephrine reuptake inhibitor, the lack of

Table 7. Patients with left-sided valve dysfunction*

Patient	Age	Sex	Treatment group	Study phase	Duration of treatment	History of hypertension	Valve abnormality
A	59	M	Sibutramine	Open-label	3 weeks	Yes	Mild AI
B	53	M	Sibutramine	Open-label	13 months	No	Mild AI
C	64	F	Sibutramine	Double-blind	8 months	Yes	Mild AI
D	61	F	Placebo	Double-blind	11 months	Yes	Mild AI
E	47	M	Placebo	Double-blind	8 months	No	Severe AI

*Severity of mild or greater aortic insufficiency and/or moderate or greater mitral regurgitation.
AI, aortic insufficiency.

valvular heart disease associated with sibutramine may be the reflection of a mechanism of action which is distinct from that of the serotonin-releasing agents fenfluramine and dexfenfluramine.

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