



A clinical trial of the use of Sibutramine for the treatment of patients suffering essential obesity

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OBJECTIVE: To evaluate the safety and efficacy of Sibutramine 10 mg per os, once a day in obese patients over a period of 6 months.

DESIGN: A monocenter, double-blind, placebo-controlled, parallel, prospective clinical trial.

SUBJECTS: 109 male and female obese patients (BMI > 30 kg/m²) from 16 to 65 y entered the trial.

MEASUREMENTS: Body weight, body mass index (BMI), waist and waist/hip ratio, medical history, assessment of hunger, satiety and diet compliance, standard laboratory assessments, blood pressure, heart rate and ECG.

RESULTS: 40 out of 55 patients in the Sibutramine group and 44 out of 54 patients in the placebo group completed the trial. Using the method of last observation carried forward (LOCF), the weight loss in the Sibutramine group was 7.52 kg (95% confidence intervals (95% CI) 6.15; 8.9) and that in the placebo group was 3.56 kg (95% CI 2.41; 4.7). The BMI loss was 3.14 kg/m² (95% CI 2.58; 3.69) in the Sibutramine group and 1.46 kg/m² (95% CI 0.99; 1.93) in the placebo group. The waist reduction was 12.51 cm (95% CI 9.25; 15.77) in the Sibutramine group and 3.26 cm (95% CI 1.38; 5.14) in the placebo group ($P < 0.05$ by paired Student's *t*-test for all the intragroup comparisons). 32 Sibutramine patients had 45 adverse events, the most frequent adverse events in the Sibutramine group being dry mouth ($n=19$), increase in blood pressure ($n=5$), constipation ($n=5$) and tachycardia ($n=5$); 23 placebo patients had 29 adverse events, mainly increase in blood pressure ($n=11$) and dry mouth ($n=10$). Two Sibutramine patients withdrew from the trial due to adverse events.

CONCLUSION: Sibutramine induces significant loss of body weight, BMI and waist, but does not significantly affect cardiovascular function. Sibutramine was well tolerated by most of the patients.

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Keywords: obesity treatment; Sibutramine; double blind; placebo controlled; clinical trial

Introduction

Obesity is a chronic disease which has become one of the most serious health problems in the world.^{1–3} In fact, obesity is a major determinant of many non-communicable diseases⁴ and induces non-insulin-dependent diabetes,⁵ coronary heart disease⁶ and stroke.⁷

A minimal weight loss induces significant health benefits in obese patients,⁸ but the maintenance of weight loss is very difficult and most of the patients tend to regain weight.^{9,10} The recognition of this problem has led to an approach of long-term treatment for obesity, including drug therapy, similar to other chronic diseases.^{9,11,12}

Sibutramine has been approved for the long-term treatment of obesity by the Health Authorities in USA, Mexico and Brazil and was recently registered in Switzerland and Germany. Sibutramine is a serotonin

and noradrenaline reuptake inhibitor with no effect on the dopamine reuptake system,¹³ and no addictive potential.¹⁴ Animal studies show that Sibutramine induces weight loss by enhancing satiety and increasing the metabolic rate.^{13,15}

Three clinical trials of the effect of Sibutramine have been extensively reported up to this moment. Weintraub *et al* reported a dose-dependent weight loss induced by Sibutramine over 8 weeks of treatment; the weight loss achieved was 3% for the 5 mg group and 5.1% in the 20 mg group.¹⁶ Bray *et al* found that Sibutramine produced dose-dependent weight loss in obese patients over a 24-week period, with doses ranging from 5 to 30 mg. The weight loss was 3–9% of the initial weight and 28–62% of the patients lost at least 5% of the initial body weight. The reported adverse events were dry mouth, anorexia, constipation and insomnia, and were also dose-dependent.¹⁷ Hanotin *et al*¹⁸ described another dose range study for 12 weeks with similar results. Weight loss was dose-dependent. The proportions of patients achieving a weight loss of at least 5% of their initial body weight were 23% for 5 mg, 49% for 10 mg and 55% for 15 mg. The adverse events associated with Sibutramine were dry mouth, insomnia and constipation, and were more frequent in the 15 mg group.

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An unpublished Mexican trial comparing Sibutramine 15 mg vs placebo in a double-blind model found (using the method of last observation carried forward) that weight loss in the Sibutramine group was 10.27 kg (95% CI 7.66; 13.07), corresponding to 11.8% of the initial body weight, with 37/51 (72.55%) patients losing at least 5% of the initial body weight. The most frequent adverse events were upper respiratory tract infections and constipation (Dr Guillermina Martínez, personal communication).

The aim of this trial was to evaluate the safety and efficacy of Sibutramine, 10 mg, in obese patients included in a program of dietary advice over a period of 6 months.

Methods

A double-blind, placebo-controlled, parallel group, prospective clinical trial was conducted in order to assess the safety and efficacy of Sibutramine in the treatment of obesity in Mexican patients.

Male and female patients from 16 to 65 y with a BMI greater than 30 kg/m² were recruited after written informed consent had been obtained. The following patients were not included in the trial: those suffering from endocrine diseases other than type 2 diabetes mellitus, those with uncontrolled hypertension, autoimmune diseases, ischemic heart disease or arrhythmia, lactating or pregnant women, those with psychosis, and those requiring drugs acting on the central nervous system, cathartics, thyroid replacement or diuretics.

Patients' participation was stopped if they became pregnant, presented with a concomitant severe disease, suffered severe adverse events, withdrew their informed consent or failed to attend the clinical appointments.

Based on previous results we expected¹⁷ that patients taking 10 mg of Sibutramine for 24 weeks would lose 6.19 ± 0.69 kg (mean \pm s.e.). Using the sample size calculation described by Glantz,¹⁹ the sample size was 20 per group. A loss of 5% of the initial body weight was considered clinically significant. We decided to admit 110 patients to the study. The subjects were outpatients attending to the Endocrinology Service, Hospital General de México.

Patients were randomized either to the group taking Sibutramine 10 mg per os, once a day or to the group taking placebo in the same way. In order to randomize the participants, we prepared a computer list of 120 random numbers in 12 different blocks of 10. For each block the proportion of even/odd numbers by group was 3/2 or 2/3, with no more than three consecutive positions. The patients were assigned a consecutive number as they completed the initial laboratory safety test and an electrocardiogram to confirm the selection criteria. For each number there was a box containing

19 packages with 10 capsules each (two blisters of five capsules), and an opaque sealed envelope with the drug code; all the materials for a patient were identified by the patient number. The materials were prepared by AB, who did not know the identity of the patients. GF received the trial materials without any knowledge of the procedures or order in the random number list. The first patient entered the trial in March 1998 and the last patient had finished the trial by November 1998.

The appearances of all the boxes, packages, blisters and capsules were the same.

Patients were recommended to complete a diet of 30 kcal/kg of the ideal body weight, the diet having about 50% of the energy from carbohydrates, 30% from lipids and 20% from proteins. Patients received a list of recommended food portions and the possible combinations.

Patients received the dietetic advice 15 days before the beginning of the medications and the dietetic supervision during the treatment phase of the trial.

Clinical control visits were 15 days before the beginning of the study medication, when the medication began, and then monthly, for up to 6 months of treatment.

The primary end-points for the trial were the body weight and BMI; the secondary end-points were the waist circumference and waist/hip ratio. Appetite, satiety and diet adherence were also evaluated. For appetite, the visual analog scale was a line of 155 mm with 10% divisions from 0% with the quotation 'very hungry' on the left, up to 100% 'without hunger' to the right. In the case of satiety the scale was similar but the 0% mark on the left corresponded to the legend 'extremely full' and the right mark of 100% to 'emptiness sensation'. The scale for compliance with the diet had the legend 'impossible to follow' corresponding to 0% on the left and 'easy to comply' on the right mark of 100%. All the described parameters were evaluated at each visit.

Adverse events were reported as they were detected. Patients were encouraged to call the investigators if they had any question or complaint at any time. Additionally, the patients were asked if 'something unusual had happened since your last visit' at all the visits, in order to collect any possible complaints from the patients.

Blood cytology, blood chemistry and urinalysis were performed before the beginning of the medication and after 6 months of medication. Electrocardiograms were performed at these times, too.

The proposed statistical analysis for the end-points included the intent-to-treat analysis of variance for repeated measures looking for the effect of repetition and for the interaction between repetition and study medication, and the intragroup comparison of the values at the baseline with those in the last visit by the paired Student's *t*-test. The same kind of analysis was performed with the last observation carried forward (LOCF) of the end-points, where the last obser-

vation replaced the missing values. For this analysis, only patients who completed at least 1 month of treatment with the corresponding end-point evaluation were considered.

After the editorial commentary by Williamson²⁰ criticizing the LOCF analysis to compensate for missing data from the drop-outs on an Orlistat trial, we decided to make a complementary analysis assuming that the dropped-out patients were non-responders (losing less than 5% of the initial body weight). The missing data were calculated using regression curve estimation obtained from the non-responders' data.²¹

The rate of patients achieving the 5 and 10% loss from the baseline in each group was compared using the Kaplan–Meier statistics, including the inverse of the Survival Curve. The odds-ratio calculations for the 5 and 10% responders were also planned.

For the rest of the interval measurements, the intragroup comparisons were tested by the paired Student's *t*-test, while the intergroup comparisons were performed using the unpaired Student's *t*-test and, in the case of nominal scales in the intergroup comparisons, the chi-square test was used, with continuity correction in the 2×2 tables.

The protocol was approved by the local investigation and ethics committee and the Mexican Ministry of Health. The protocol complied with the Mexican regulations and with the European Good Clinical Practice guidelines.

Results

A total of 110 subjects were considered to enter the trial, but one patient was not included because the electrocardiogram showed subendocardial ischemia. Thus, 109 patients started the trial medication.

The patients' demographics are described in Table 1. Both groups are statistically similar, so the randomization and concealment were considered successful. Based on the empty blisters, the compliance of the patients was considered to be at least 90%. The

Table 1 Characteristics of the patients at the beginning of the study

	Sibutramine	Placebo	P
<i>n</i>	55	54	
Sex:			0.706 ^a
Male(%)	4(7.3)	5(9.3)	
Female(%)	51(92.7)	49(90.7)	
Age(y); mean±s.d.	38.09±10.11	39.48±10.26	0.478 ^b
Weight(kg); mean±s.d.	87.53±16.0	86.41±12.92	0.688 ^b
Height(cm); mean±s.d.	155.29±6.45	156.02±6.58	0.561 ^b
BMI(kg/m ²); mean±s.d.	36.14±5.07	35.51±4.99	0.519 ^b

Statistical tests used: ^achi-square with continuity correction; ^bunpaired Student's *t*-test.

evolution of the end-points, body weight, BMI and waist circumference and waist-to-hip ratio, expressed as means±s.d., is given in Table 2

Forty out of 55 patients in the Sibutramine group and 44 out of 54 patients in the placebo group completed the trial. The effects of the trial medication on the end-points are shown in Table 3. The Sibutramine group achieved important, significant reductions considering the intent-to-treat and the LOCF analysis.

The intent-to-treat Anova for multiple measures of the body weight, BMI and waist circumference showed the effect of time (months) and interaction of the effect of time with the kind of medication (*P* < 0.001). For the waist-to-hip ratio, the analysis showed the effect of the time (*P* < 0.001), but not of the medication (*P* > 0.05).

The Anova for repeated measures using LOCF produced similar results to the intent-to-treat analysis. Figure 1 shows the absolute reduction in the body weight using LOCF.

In the intent-to-treat analysis, the number of patients losing 5% of their initial body weight was 34/40 (85%) for the Sibutramine group and 21/44 (47.7%) in the control group. Considering the LOCF, the number of patients reaching the 5% goal was 37/51 (72.55%) for the Sibutramine group, and 21/52 (40.4%) in the placebo group. The odds-ratio for the Sibutramine group to achieve the 5% goal was 1.8 (95% confidence limits, CI, 1.24; 12.6).

Table 2 Data for the endpoints

	Day-15	Day 0	Day 30	Day 60	Day 90	Day 120	Day 150	Day 180
<i>N</i> Sibutramine	55	55	51	47	48	42	41	40
<i>N</i> Placebo	54	54	52	50	45	44	41	44
Body weight	87.53±16.0	86.18±15.63	83.32±15.65	81.37±15.53	80.28±15.55	78.85±15.27	78.73±15.28	78.77±15.47
Sibutramine								
Body weight placebo	86.41±12.92	85.08±12.84	84.56±13.17	83.41±13.38	83.12±13.32	82.05±12.06	82.20±13.49	81.84±13.49
BMI Sibutramine	36.14±5.07	35.58±4.95	34.38±4.85	33.56±4.78	33.17±4.78	32.73±4.77	32.56±4.83	32.52±4.87
BMI placebo	35.51±4.99	34.97±5.02	34.72±5.21	34.31±5.37	33.97±5.51	33.64±5.14	33.31±5.19	33.25±5.10
Waist circumference	103.54±13.43	102.29±12.6	99.78±12.09	98.10±11.57	96.92±11.74	96.11±11.54	94.78±10.87	94.93±11.18
Sibutramine								
Waist circumference placebo	103.04±13.71	102.02±13.36	101.33±13.94	99.64±13.33	99.42±13.43	98.79±13.39	98.52±13.70	97.40±13.24
Waist-to-hip ratio	0.88±0.08	0.88±0.07	0.87±0.07	0.87±0.06	0.86±0.06	0.86±0.06	0.85±0.06	0.85±0.06
Sibutramine								
Waist-to-hip ratio placebo	0.89±0.08	0.88±0.07	0.88±0.07	0.87±0.08	0.87±0.07	0.87±0.07	0.87±0.07	0.86±0.07

Table 3 Effect of the trial medication on the end-points

	Intent-to-treat (6 months completers)		LOCF	
	Sibutramine	Placebo	Sibutramine	Placebo
Weight (kg)				
mean change	8.61	4.03	7.52	3.56
(95% CI)	(7.06; 10.17) ^a	(2.74; 5.32) ^a	(6.15; 8.9) ^a	(2.41; 4.7) ^a
Percentage of the baseline weight				
mean ± s.d.	90.11 ± 4.94	95.23 ± 5.01	91.33 ± 5.11	95.81 ± 4.85
(95% CI)	(88.66; 91.56) ^a	(93.83; 96.64) ^a	(90.0; 92.67) ^a	(94.56; 97.06) ^a
BMI (kg/m ²)				
mean change	3.59	1.66	3.14	1.46
(95% CI)	(2.97; 4.22) ^a	(1.12; 2.19) ^a	(2.58; 3.69) ^a	(0.99; 1.93) ^a
Waist circumference (cm)				
mean change	8.09	4.69	6.81	4.35
(95% CI)	(5.88; 10.29) ^a	(3.11; 6.27) ^a	(4.78; 8.83) ^a	(2.93; 5.78) ^a
Waist-to-hip ratio				
mean change	0.021	0.028	0.017	0.025
(95% CI)	(0.005; 0.038) ^a	(0.014; 0.043) ^a	(0.003; 0.031) ^a	(0.012; 0.038) ^a

^aIntragroup comparison vs baseline assessment $P < 0.05$ by paired Student's t -test.

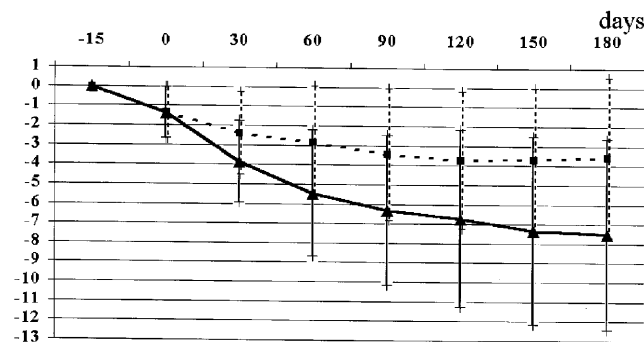


Figure 1 Body weight reduction throughout the trial using LOCF. The figure represents the mean ± s.e.m. of the absolute weight loss in kg at the different times of the study. The solid line corresponds to the Sibutramine group and the broken line to the placebo group.

The endpoint weight correlated well with the baseline body weight ($r > 0.95$) in the non-responders, when considering Sibutramine and control groups together. Assuming the worst case scenario for the dropped-out patients, they would be non-responders. Using regression curve estimation we calculated the predicted weights for the non-responder completers and for the dropped-out patients.

The calculated values for the non-responder completers are very close to the observed values: the ratio of calculated/observed (\pm s.d.) is 100.03 ± 1.99 , lowest value 96.2, and highest value 103.37.

The final mean weight, including the predicted weight for the dropped-out patients, was 80.88 ± 15.84 kg for the Sibutramine group, and 82.86 ± 13.63 kg for the placebo patients. The final weights according to LOCF were 79.65 ± 15.77 and 83.4 ± 13.66 kg for the Sibutramine and placebo groups, respectively.

In the intent-to-treat analysis, the rate of patients losing 10% of their initial body weight was 18/40 (45%) in the Sibutramine group and 4/44 (9.1%) in the control group. Considering the LOCF, the number of patients reaching the 10% goal was 19/51 (37.3%)

in the Sibutramine group, and 4/52 (7.7%) in the placebo group. The odds-ratio for the Sibutramine group to achieve the 10% goal was 4.84 (95% CI 1.77; 13.25).

Figure 2 shows the cumulative rate of patients reaching the 5% weight loss goal throughout the study. It corresponds to the inverse of the Kaplan–Meier Statistics Survival Curve. The difference in the cumulative incidence of the event (5% loss of the initial weight) is significant ($P < 0.01$ by the Log Rank, Breslow and Tarone–Ware tests for both goals). Similar figures were obtained for the 10% responders.

On the visual analog scales, patients on Sibutramine reported decreased appetite from the first month of treatment through to the end of the trial, increase of satiety in the first 3 months and a better compliance with the diet on the first month of treatment. On the other hand, the placebo group had less appetite on the first and fifth month of treatment and did not have any significant changes in satiety or diet adherence. The initial appetite score for the Sibutramine group was 64.04 ± 31.64 mm and it increased significantly

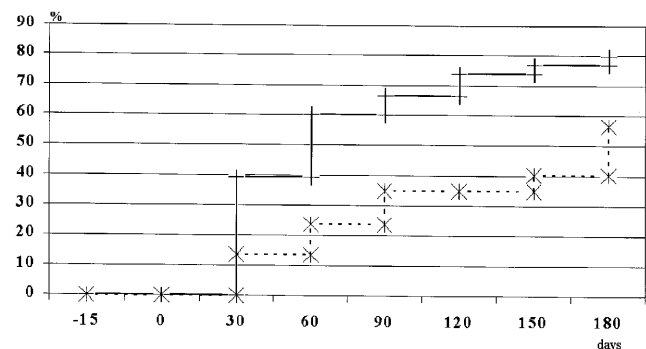


Figure 2 Kaplan–Meier statistics graphic of the cumulative incidence of 5% responders. The graphics depicts the cumulative rate of patients that achieved the 5% loss of their initial body weight throughout the study. The solid line corresponds to the Sibutramine responders; the broken line with asterisk markers to the placebo responders.

(meaning appetite reduction) from the first month of treatment through the end of the trial. For the placebo group the initial score was 64.53 ± 30.16 mm, and it only had significant increments in the first and the fifth month of treatment.

Anova for repeated measures for systolic and diastolic blood pressure did not show any effect of the treatment groups, nor any of the time (different assessments), nor interaction of treatment groups with time ($P > 0.05$); see Table 4.

Considering the heart rate, Anova for repeated measures showed an effect of the time (different assessments; $P < 0.05$), but not of the treatment groups, nor interaction of treatment groups with time ($p > 0.05$); see Table 4.

The paired electrocardiograms did not show significant variations in the Sibutramine group. Placebo patients had small but statistically significant changes in heart rate (78.9 ± 9.3 vs 72.2 ± 11.2 bpm), and ST segment (11.6 ± 1.2 vs 12.2 ± 1.83 ms; $P < 0.05$ by paired Student's *t*-test).

Regarding the clinical laboratory tests, the intragroup analysis (before vs after) showed significant differences in monocytes, uric acid, creatinine, calcium, cholesterol, triglycerides, HDL, LDL and TGP for the Sibutramine group. The placebo group presented significant changes in uric acid, creatinine, calcium and alkaline phosphatase; see Table 5

Table 6 describes the adverse events during the trial. In all, 31 patients in the Sibutramine group

experienced 45 adverse events, the most frequently reported being dry mouth (19 cases), significant increase of blood pressure,⁵ constipation,⁵ and tachycardia.⁵ A total of 32 adverse events happened during the first month of treatment and nine in the second.

Table 6 Adverse events presented

	Sibutramine	Placebo
Dry mouth	14	10
Significant increase in blood pressure	5	11
Significant increase in heart rate	5	1
Constipation	5	-
Insomnia	2	-
Urinary tract infection	1	2
Headache	1	1
Hypersomnia	1	1
One case of each:	Dry mouth, dizziness headache, face paresthesia Constipation, dry mouth Insomnia, dry mouth Herpes Muscular cramps Dry cough Asthenia Dizziness and possible blood hypotension Multiple ecchymosis Face dermatitis Dry mouth and arm paresthesia, weighty sensation in head	Diaphoresis Meteorism Dermatosis

Table 4 Evolution of the systolic and diastolic blood pressure and heart rate

	Days							
	-15	0	30	60	90	120	150	180
Systolic blood pressure^a								
Sibutramine	115.1 ± 9.57	116.73 ± 6.03	116.08 ± 10.21	115.74 ± 10.88	113.33 ± 9.96	115.0 ± 8.41	116.46 ± 8.0	116.75 ± 8.51
Placebo	119.54 ± 11.75	117.78 ± 8.72	120.19 ± 10.29	117.65 ± 9.47	115.76 ± 9.83	115.89 ± 9.43	114.52 ± 9.16	115.57 ± 7.41
Diastolic blood pressure^a								
Sibutramine	76.73 ± 6.17	76.18 ± 5.35	77.84 ± 5.85	77.13 ± 5.97	76.46 ± 9.96	77.62 ± 5.44	76.83 ± 5.56	77.0 ± 6.68
Placebo	78.98 ± 6.32	78.61 ± 6.1	78.08 ± 7.49	77.35 ± 7.08	78.15 ± 7.25	77.78 ± 6.18	76.43 ± 6.56	77.53 ± 5.88
Heart rate^b								
Sibutramine	76.02 ± 7.26	73.73 ± 4.51 ^a	75.31 ± 5.82	76.28 ± 5.58	75.74 ± 5.8	75.05 ± 3.68	75.32 ± 3.55	75.88 ± 4.4
Placebo	77.33 ± 8.24	74.8 ± 5.1	75.46 ± 5.39	76.84 ± 4.61	75.58 ± 4.81	75.51 ± 4.3	74.79 ± 4.15	75.18 ± 4.23

^aThe Anova for repeated measures did not show the effect of the treatment groups, nor the effect of the time (different assessments), nor interaction of treatment groups with time ($P > 0.05$).

^bThe Anova for repeated measures showed the effect of the time (different assessments; $P < 0.05$), but not of the treatment groups, nor interaction of treatment groups with time ($P > 0.05$).

Table 5 Clinical laboratory parameters with significant changes (mean ± s.d.)

	Sibutramine	Placebo
Monocytes	1.19 ± 0.87	1.82 ± 0.85**
Uric acid	4.70 ± 0.99	4.16 ± 0.65*
Creatinine	0.90 ± 0.13	0.86 ± 0.15*
Calcium	9.66 ± 0.58	9.21 ± 0.76*
Cholesterol	201.02 ± 34.53	193.23 ± 30.54*
Triglycerides	197.93 ± 167.6	142.31 ± 63.97**
HDL	41.56 ± 8.80	49.55 ± 10.73*
LDL	119.87 ± 28.16	113.63 ± 25.72*
TGP	34.15 ± 19.52	26.75 ± 10.39*
Alkaline Ph	103.16 ± 34.47	102.82 ± 33.5

* $P < 0.05$ by Student's *t*-test.

** $P < 0.05$ by Student's *t*-test and Wilcoxon test.

Patients 9 to 109 stopped the trial medication due to the adverse events of dry mouth and paresthesia of lips and arm, respectively.

In contrast, 23 patients in the placebo group had 29 adverse events, the most common being significant increase of blood pressure in 11, and dry mouth in 10. Patient no. 92 stopped the trial because of severe dermatosis as a concomitant disease.

Forty patients in the Sibutramine group finished the trial, and 44 in the placebo group. Eleven (20%) Sibutramine patients were lost to follow-up, as well as nine (16.67%) placebo patients. Two Sibutramine patients and one placebo patient left the trial due to adverse events.

As part of a crossover design in the second part of the trial we were able to follow some patients who were in Sibutramine for 6 months after the end of the medication. This group of patients was on diet and medical support without medications. Three months after they stopped the drug their weight had increased by 2.21 ± 2.46 ; 1.5 kg (mean \pm s.d.; median), which is equivalent to 2.78 ± 2.99 ; 2.25 percentage points of the weight at the end of the drug treatment.

Discussion

Obesity is a serious medical condition which should be treated with the same approach as other chronic diseases. The main goal of the treatment should be maintaining a long-term healthy weight according to age, sex and physiological condition in order to avoid health risks.¹²

Benefits of weight loss have been shown for the comorbidities associated with obesity.⁸ Yet, after an initial successful weight loss the most of the patients tend to regain body weight.⁹ As for other chronic conditions, new pharmacological agents have been tried to improve the successful rate on a long-term weight maintenance.

Sibutramine is a new drug approved for the longer-term treatment of obesity. The pharmacological profile of Sibutramine implies the action on the serotonin and noradrenaline system with effects on satiety and metabolic rate.¹³ Previously, the safety and efficacy of Sibutramine have been reported in dose range trials. The effect of therapy of 15 mg per day for 12 weeks was a reduction of 4.9 ± 0.5 kg, with 55% of the patients losing at least 5% of their initial body weight,¹⁶ and over a 24 week treatment period, a weight loss of 7.68 ± 1.56 kg (male patients) with 52% of the patients losing at least 5% of their initial body weight.¹⁷

In a previous trial with Mexican patients using Sibutramine 15 mg OD, patients had a weight loss of 7.07 ± 4.94 kg (95% CI 5.34; 8.8), with 23/34 (67.6%) patients achieving the 5% goal (LOCF values) by the third month of medication.

After 6 months of treatment, the weight loss in the Sibutramine patients was 10.37 ± 7.76 kg (95% CI 7.66; 13.07), with 26/34 (76.5%) patients reaching the 5% goal (LOCF values; Dr Martinez, personal communication).

In the trial reported here the Sibutramine patients achieved a weight loss of 7.52 kg (95% CI 6.15; 8.9) with 37/51 (72.5%) patients losing at least 5% of the initial body weight (LOCF values). Sibutramine patients had improvements in the lipid profile, especially those suffering from dyslipidaemia. Placebo patients had a good response to the treatment, close to a 5% loss of the initial body weight, presumably because of the strong dietary advice and patient support.

The profile of the adverse events observed was related to the mode of action of the drug and reflects the activation of the sympathetic nervous system. Most of the adverse events in the Sibutramine group occurred in the first 2 months of treatment. The experience of adverse events could lead to the suspicion that these patients were on Sibutramine rather than placebo.

No important cardiovascular effects related to the study drug were found. Previous studies²² have found 2 mmHg increases in systolic and diastolic blood pressures in the patients taking 10 or 15 mg of Sibutramine, with an increase of 3–6 beats per minute in heart rate. In the present study, the mean blood pressure did not change significantly, and only four patients had a clinically significant increase. Heart rate did not increase significantly during the treatment, and only three patients had transitory heart rates higher than 90 bpm. Thus, the cardiovascular tolerance was good and is unlikely to be a serious limitation to extending the period of treatment.

We concluded that Sibutramine induces significant loss of body eight, BMI and waist circumference, but does not significantly affect cardiovascular function, and that it was well tolerated by most of the patients.

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