

Tolerability and Effectiveness of Fluoxetine, Metformin and Sibutramine in Reducing Anthropometric and Metabolic Parameters in Obese Patients

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ABSTRACT

The aim of this study is to assess the effects of sibutramine (S) 15 mg/day, fluoxetine (F) 60 mg/day, and metformin (M) 1,700 mg/day, as an adjunct therapy to a 1,500 kcal/day diet, in reducing anthropometric and metabolic parameters. S (n= 8), F (n= 9), and M (n= 8) were compared to placebo (n= 10) in 35 obese patients in a 90-day trial. Side effects were also studied during the treatment. The data demonstrated that F therapy resulted in a greater average reduction in BMI (11.0%), weight (10.0%), abdominal circumference (11.0%) and %fatty-tissue (12.8). An elevation in HDL-cholesterol (25.8%) and a reduction in average triglyceride levels (28.3%) were also shown. S presented a 7.91% reduction in the abdominal circumference and a 9.65 reduction in %fatty-tissue was also found. M group presented reductions in BMI (4.03%), waist circumference (6.92%), HOMA (23.5%) and blood pressure (6.08% in systolic and 2.08% in diastolic). In general, the three drugs can be considered well tolerated. We concluded that F and S demonstrated a greater mean reduction in anthropometric and metabolic parameters when compared to M, however all of them are useful for that purpose, when the subjects' characteristics are considered. (**Arq Bras Endocrinol Metab 2006;50/6:1020-1025**)

Keywords: Fluoxetine; Metformin; Obesity; Sibutramine; Side effects

RESUMO

Tolerabilidade e Eficácia da Fluoxetina, Metformina e Sibutramina na Redução de Parâmetros Antropométricos e Metabólicos em Pacientes Obesos.

O objetivo deste estudo foi avaliar o efeito da sibutramina (S) 15 mg/dia, fluoxetina (F) 60 mg/dia, e metformina (M) 1.700 mg/dia, associadas a uma dieta de 1.500 kcal/dia, na redução de parâmetros antropométricos e metabólicos. S (n= 8), F (n= 9) e M (n= 8) foram comparadas ao placebo (n= 10) em 35 pacientes obesos durante 90 dias de tratamento. As reações adversas também foram avaliadas durante o tratamento. O grupo F demonstrou uma redução no IMC (11,0%), peso (10,0%), circunferência abdominal (11,0%) e % de tecido adiposo (12,8). Também foram observados um aumento nos níveis de HDL-colesterol (25,8%) e uma redução nos níveis de triglicérides (28,3%), no grupo F. O grupo S apresentou uma redução de 7,91% na circunferência abdominal e de 9,65 na % de tecido adiposo. Já o grupo M apresentou reduções no IMC (4,03%), circunferência abdominal (6,92%), HOMA (23,5%) e pressão arterial (6,08% na sistólica, 2,08% na diastólica). Os três fármacos analisados foram bem tolerados durante o tratamento. Concluímos que a F e a S demonstraram maior eficácia na redução dos parâmetros antropométricos e metabólicos dos pacientes obesos quando comparadas à M, entretanto todas podem ser prescritas para essa finalidade, desde que sejam consideradas as características individuais dos pacientes. (**Arq Bras Endocrinol Metab 2006;50/6:1020-1025**)

Descritores: Fluoxetina; Metformina; Obesidade; Sibutramina; Reações adversas

OBESITY HAS BEEN DEFINED in different ways over time, such as "excessive body fat" or "weight 20% above the ideal value". However, the literature itself does not provide an accurate definition of what either "ideal" or "excess" is (1,2).

Obesity is a "chronic disease characterized by excessive fat accumulation to such an extent that will compromise the health of an individual", and is generally related to incorrect eating habits, a sedentary life style and a consumption of highly caloric food (3).

The World Health Organization (WHO) classifies overweight and obesity by using body mass index (BMI). A BMI over 25 kg/m² is defined as overweight, and a BMI of over 30 kg/m² as obese (4).

Overweight and obesity have become a world epidemic (5), which affects all ages and socioeconomic groups in both developed and developing countries (4). The International Obesity Task Force (IOTF) estimates that about 1.7 billion individuals all over the world may be overweight or obese (6).

A recent study reported that 26% of Americans are considered obese and 35% are classified as overweight. This fact shows that during the last decades, the prevalence of obesity has increased dramatically all over the world (7).

In Brazil, according to the Brazilian Institute of Geography and Statistical (IBGE), 40.6% of the subjects with age over 20 years are overweight, and 11% of them are obese. In 2003, 41.1% and 8.9% of the adult men and 40% and 13.1% of the adult women were overweight and obese, respectively (8).

Obesity can be evaluated by anthropometric methods (9), especially BMI, considered a practical, fast and low cost method that can be used to estimate the total amount of body fat (10). However, a limitation of the BMI is that it does not differentiate between muscle and fatty tissue (11). Nevertheless, it is a method extensively used in international studies, regarded as quite reliable when used together with the measurements of abdominal circumference and bioimpedance.

Laboratory methods such as blood count and the determination of urea, creatinine, uric acid, glycemia, total cholesterol, cholesterol fractions and triglycerides are also used for the evaluation of comorbidities associated with obesity (9).

Some patients have proved to be completely impotent and dissatisfied with the conventional treatment based on dietary reeducation and physical activity. In addition to that, pharmacological treatment, after being ignored for many years, is currently attracting more and more interest and is believed to become the best modality available for the obesity treatment

(12). That treatment, however, is only recommended as a part of an overall weight reduction program, together with some changes in lifestyle (13,14). Pharmacotherapy is also stimulated by the progresses in the understanding of the biological basis of body weight regulation, and has proved to be safe and effective in maintaining weight over a long period of time (15), mainly when a new generation of anti-obesity drugs, such as sibutramine and orlistat, among others, are prescribed.

Sibutramine inhibits the reuptake of serotonin and norepinephrine and this sympathomimetic drug was approved by the FDA for the chronic use in obesity treatment and was brought to the market in 1998 (16).

Fluoxetine, a drug approved for use in the treatment of depression, acts specifically by blocking reuptake of serotonin (5-HT), a neurotransmitter which is believed to reduce food intake (17), at nerve endings (18). It is also postulated that fluoxetine could either generate a reduction in body weight gain by inhibiting neuropeptide Y (NPY) action in the paraventricular nucleus of the hypothalamus, where NPY presents its hyperphagic effects (19,20).

Metformin is an oral antidiabetic drug used in the treatment of Diabetes Mellitus Type 2, which acts decreasing the glucose production by the liver and increasing the peripheral glucose uptake through the elevation of the number of insulin receptors (21). The mechanism by which metformin could reduce food intake is unknown but it is postulated that the reduction in the insulin resistance promotes some changes in energy balance that could reduce the daily caloric necessity of the individual and, as a result, a minor consumption of food (22).

A survey of the literature has shown that there is a need for new anti-obesity drugs, posing a challenge to researchers to find more effective and safer medicines for the treatment of this disease.

In this context, the main objective of the present study was to assess the tolerability and effectiveness of fluoxetine, sibutramine and metformin in reducing anthropometric and metabolic parameters in obese patients, and to compare them to placebo.

SUBJECT AND METHODS

This study was randomized and single blind, and was conducted on 35 obese patients aged 18 to 51 years old, 31 women and 4 men divided into four groups. Before the beginning of the study, all patients were given treatment with dietary reeducation for 6

months, but it was unsuccessful in reducing their body weight. All patients selected for the study had a BMI of more than 30 kg/m², inasmuch as pharmacological treatment is recommended only for patients with a BMI above 30 kg/m² or above 27 kg/m² when associated with co-morbidities such as dyslipidemia, hypertension, diabetes, osteoarthritis and sleep apnea (23).

Alcoholic patients, diabetic patients, pregnant and nursing women, as well as patients with acquired immunodeficiency and those with viral liver infections were all excluded from the study. The study protocol was approved by the Research Ethics Committee of the University of Ribeirão Preto. The volunteers were included in the study after receiving detailed information about it and signing a free and informed consent form.

Before the study, each patient was submitted to anthropometric, haemodynamic and metabolic evaluations (weight, height, BMI, abdominal circumference, blood pressure, %fatty-tissue, glucose, urea, creatinine, uric acid, total cholesterol, LDL-cholesterol, HDL-cholesterol, insulin, HOMA, urine-I, AST, ALT, and Gama-GT). All selected patients received a plan of dietary reeducation containing, on average, 1,500 calories per day.

After being considered eligible for the study, the patient was assigned to a group receiving sibutramine (15 mg/day Reductil[®], lot 901308F01), metformin (1700 mg/day Glifage[®], lot 1021133), fluoxetine (60 mg/day Daforin[®], lot 04G089) or placebo (3 tablets/day). The treatment started and the patient was monitored by interviews held on the following days: zero, 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, 84, and 90. Anthropometric, haemodynamic and metabolic evaluations were performed on days zero, 42 and 90.

Weight (kg) and height (m) were measured with a Filizola[®] anthropometric scale. BMI was obtained by the ratio of weight (kg) to height (m) squared (9). The patients were always weighed while wearing only a hospital gown.

According to WHO recommendations, the abdominal circumference is measured half way between the last rib and the iliac crest in the position of inspiration using a measuring tape (9,24,25).

Arterial pressure was measured with an Oxigel[®] sphygmomanometer, always at the same time of the day. The percentage of fatty tissue was assessed by bioelectric impedance using a model 101-A RJL Prizum apparatus with TBW electrodes (4).

The tests were performed using the GraphPad Instat[®] and Statgraphics[®] software for analysis of the

means (ANOVA), Student t-test and multiple comparisons between groups (Tukey-Kramer test), with the level of significance set at $p < 0.05$.

RESULTS

The data demonstrated that fluoxetine therapy resulted in a greater average reduction in BMI (11.0%), weight (10.0%), abdominal circumference (11.0%) and %fatty tissue (12.8) (table 1). An elevation in HDL-cholesterol (25.8%) and a reduction in average triglyceride levels (28.3%) were also shown, when compared with the other three drugs (table 2). Sibutramine presented a 7.91% reduction of the abdominal circumference and a 9.65% reduction in %fatty-tissue (table 1). Metformin presented reductions in BMI (4.03%), waist circumference (6.92%), HOMA (23.5%) and blood pressure (6.08% in systolic and 2.08% in diastolic) (tables 1 and 2). The placebo group presented a significant increase ($p > 0.05$) in insulin levels of 95.1% (table 2).

In the sibutramine group, the side effects most often reported by the patients were mouth dryness (79.2%), constipation (41.7%), sudoresis (45.8%), insomnia (20.8%) and headache (16.7%). In the metformin group, the main side effects reported were diarrhea (45.8%), mouth dryness (37.5%), sudoresis (29.2%), vertigo (29.2%), nausea (25.0%) and altered palate (20.8%).

In the fluoxetine group, the adverse reactions more commonly reported by the patients were anorexia (92.6%), insomnia (29.6%), sleepiness (29.6%), nausea (14.8%) and sexual dysfunction (11.1%), while in the placebo group, the adverse reactions more commonly reported were anorexia (13.3%), thirst (6.7%) and diarrhea (6.7%).

DISCUSSION

Sibutramine was prescribed at a dose of 15 mg/day and was administered daily at about 9:00 a.m., a time considered safe to prevent episodes of insomnia. The usual initial dose of sibutramine is 10 mg/day; however, we opted for 15 mg/day because, according to Gokcel et al. (9), patients who receive 10 mg/day report hunger during the night. The metformin dose prescribed to the patients was 1,700 mg/day, divided into two administrations of 850 mg, the first a few minutes after lunch and the second after dinner. This dose has been reported to be safe and effective in pro-

Table 1. Anthropometric and hemodynamic parameters (average \pm SD) of obese patients before and after the pharmacological treatment.

Parameters	SIBUTRAMINE			METFORMIN			FLUOXETINE			PLACEBO		
	BEFORE	AFTER	%	BEFORE	AFTER	%	BEFORE	AFTER	%	BEFORE	AFTER	%
Age (years)		30.2			38.9			30.9			31.4	
Height (m)		1.63			1.61			1.60			1.56	
Weight (kg)	84.5	78.7	-6.86 ^{ns}	95.5	91.9	-3.77 ^{ns}	92.3	83.0	-10.0 ^{ns}	78.7	77.7	-1.30 ^{ns}
	(\pm 6.998)	(\pm 6.774)		(\pm 14.14)	(\pm 13.44)		(\pm 10.070)	(\pm 9.016)		(\pm 9.975)	(\pm 10.657)	
BMI (kg/m ²)	32.0	29.8	-6.87 ^{ns}	37.2	35.7	-4.03 ^{ns}	36.1	32.4	-10.1*	32.2	31.8	-1.40 ^{ns}
	(\pm 2.415)	(\pm 2.701)		(\pm 5.821)	(\pm 5.556)		(\pm 3.167)	(\pm 2.555)		(\pm 3.237)	(\pm 3.432)	
Abdominal Circumference	103.7	95.5	-7.91*	117.1	109.0	-6.92 ^{ns}	111.7	99.3	-11.0*	101.4	98.5	-2.90 ^{ns}
	(\pm 4.472)	(\pm 4.552)		(\pm 14.30)	(\pm 11.08)		(\pm 6.538)	(\pm 5.196)		(\pm 5.296)	(\pm 5.720)	
P.A. (mm/Hg)	118 / 75	117 / 80	-0.08 ^{ns} / +6.67 ^{ns}	148 / 96	139 / 94	-6.08 ^{ns} / -2.08 ^{ns}	145 / 104	136 / 98	-6.29 ^{ns} / -5.16 ^{ns}	136 / 99	130 / 91	-4.94 ^{ns} / -8.59 ^{ns}
% Adipose tissue	34.2	30.9	-9.65 ^{ns}	38.6	37.9	-1.81 ^{ns}	36.4	31.7	-12.8*	34.0	34.1	+0.20 ^{ns}
	(\pm 8.049)	(\pm 8.758)		(\pm 8.535)	(\pm 8.202)		(\pm 6.135)	(\pm 2.302)		(\pm 4.818)	(\pm 7.397)	

^{ns}: not significant, $p > 0.05$; *: statistically significant, $p < 0.05$.

Table 2. Some metabolic parameters (average \pm SD) of obese patients before and after the pharmacological treatment.

Parameters	SIBUTRAMINE			METFORMIN			FLUOXETINE			PLACEBO		
	BEFORE	AFTER	%	BEFORE	AFTER	%	BEFORE	AFTER	%	BEFORE	AFTER	%
HDL-cholesterol	57.0	50.0	-12.3 ^{ns}	49.2	45.7	-7.11 ^{ns}	39.1	49.2	+25.8*	44.9	49.5	+10.2 ^{ns}
	(\pm 22.53)	(\pm 19.47)		(\pm 13.82)	(\pm 13.16)		(\pm 4.859)	(\pm 6.815)		(\pm 8.621)	(\pm 14.128)	
Triglycerides	89.2	100.2	+12.3 ^{ns}	153.0	162.6	+6.27 ^{ns}	137.9	98.9	-28.3 ^{ns}	95.5	114.2	+19.6 ^{ns}
	(\pm 19.90)	(\pm 47.71)		(\pm 90.38)	(\pm 95.23)		(\pm 55.871)	(\pm 37.866)		(\pm 49.532)	(\pm 69.477)	
Insulin	7.4	6.5	-12.1 ^{ns}	12.6	10.0	-20.7 ^{ns}	10.2	11.9	+17.1 ^{ns}	7.2	14.1	+95.1*
	(\pm 2.768)	(\pm 2.428)		(\pm 5.705)	(\pm 2.819)		(\pm 5.664)	(\pm 9.694)		(\pm 3.901)	(\pm 8.789)	
HOMA	1.70	1.51	-11.2 ^{ns}	2.98	2.38	-23.5 ^{ns}	2.04	2.436	+19.1 ^{ns}	1.59	3.01	+89.3 ^{ns}
	(\pm 0.633)	(\pm 0.542)		(\pm 1.737)	(\pm 0.837)		(\pm 1.072)	(\pm 2.039)		(\pm 0.926)	(\pm 2.268)	
Glicaemia	91.2	94.9	+4.06 ^{ns}	90.5	91.1	+0.66 ^{ns}	83.1	82.8	-0.4 ^{ns}	89.0	83.4	-6.3 ^{ns}
	(\pm 4.83)	(\pm 9.80)		(\pm 12.88)	(\pm 10.33)		(\pm 10.5)	(\pm 6.6)		(\pm 12.8)	(\pm 7.9)	

^{ns}: not significant, $p > 0.05$; *: statistically significant, $p < 0.05$.

moting anorexic effects (9,26,27). The fluoxetine dose prescribed was 60 mg/day (three tablets of 20 mg each) and was administered daily at about 9:00 a.m., after breakfast, to avoid side effects like nausea and vomiting (28). Placebo was administered in the same manner as fluoxetine.

The data of anthropometric and hemodynamic parameters are presented in table 1, which shows that, before treatment, the average BMI of the patients assigned to sibutramine, metformin, fluoxetine and placebo groups was over of 30.0 kg/m². BMI is considered to be an attractive anthropometric measure because it requires minimal training of the person who obtains it and involves a low cost procedure. BMI has some limitations because it does not distinguish between adipose tissue and muscle mass. However, it is

widely used in international studies and is quite reliable when used together with the measurement of abdominal circumference and other anthropometric methods (29-31). Table 1 shows that only fluoxetine treatment promoted a statistically significant 10.1% reduction in BMI ($p < 0.05$), while treatment with sibutramine, metformin and placebo also reduced BMI, but without statistical significance. The mean BMI reduction in the fluoxetine group permitted to change patient classification from moderately to slightly obese. Although the reduction of BMI in the sibutramine group was not considered to be statistically significant, the mean BMI at the end of the study was 29.8 kg/m², which classifies the patients as overweight instead of slightly obese. In contrast, there were no modifications in the classification of the metformin and placebo groups.

A survey of the literature has shown that the reduction of BMI promoted by fluoxetine was also described by several authors (32,33), whereas Bray et al. (23) and Gokcel et al. (9) detected a reduction in BMI in patients treated with sibutramine.

Fluoxetine and sibutramine induced a non-significant reduction in body weight. However, in agreement with the literature, even discrete losses of 5 to 15% of the patient's initial body weight produce short-term benefits regarding several medical complications related to obesity, such as diabetes type 2, hypertension and dyslipidemias.

In the present study, the average abdominal circumference of the patients in fluoxetine, sibutramine, metformin, and placebo groups was of over 102 cm and 88 cm, values considered safe for men and women, respectively (34). Abdominal obesity is an independent risk factor for morbidity and plays an important role in the development of hyperinsulinemia, insulin resistance, glucose intolerance, and dyslipidemia. Furthermore, some authors have demonstrated a correlation between abdominal circumference and cardiovascular disease. On this basis, treatment of obesity aiming at a reduction in abdominal circumference could be of great value for selected patients (35).

At the end of the present study there was a significant reduction of 11.0% and 7.91% in the average abdominal circumference of patients treated with fluoxetine and sibutramine, respectively (table 1).

As shown in table 1, mean %fatty-tissue in all groups before the pharmacological treatment was above the recommended values (20–30%). An important result shown in table 1 is that fluoxetine therapy induced a greater statistically significant ($p < 0.05$) reduction in %fatty-tissue (12.8%).

Regarding blood pressure, we emphasize that sibutramine was the only drug studied to promote a change in this parameter, elevating diastolic blood pressure by about 6.7%. This increase was not statistically significant but it may represent a risk for the patient when the drug is prescribed in an indiscriminate way.

An analysis of metabolic parameters showed that only metformin and sibutramine reduced the values of HOMA by 23.5% and 11.2%, respectively, though these data were not statistically significant ($p > 0.05$). A reduction in this parameter was also observed by Gokcel et al. (9).

Conversely, the placebo group presented an elevation of 89.3% in the values of HOMA, caused by a statistically significant ($p > 0.05$) increase in plasma insulin levels (95.1%). These findings suggest that

physical activity and dietary reeducation, considered fundamental pillars for the obesity treatment, when allied to a rational pharmacotherapy, can produce more satisfactory results.

Fluoxetine, differently from the other drugs evaluated, caused a clinical and statistical significant increase in the plasma levels of HDL, as shown in table 2, and reduced the triglyceride levels (table 2). These findings are clinically relevant because dyslipidemia is a comorbidity intimately related to obesity.

In addition to the desirable anthropometric and cardiometabolic effects of the drugs, their side effects were also assessed. Also, a large number of patients in the sibutramine group reported sudoresis and the number was even higher in the intermediate and final phase of the study. This effect may probably be intimately related to the thermogenic effect of the drug.

In general, metformin proved to be more tolerable than sibutramine and fluoxetine. On one hand, metformin demonstrated a modest reduction of anthropometric parameters. However, sibutramine presented a greater reduction in some anthropometric parameters. This drug, however, demonstrated an elevation of blood pressure, a fact that demands a special care in the prescription of this drug for patients with high blood pressure.

Finally, fluoxetine also demonstrated a greater reduction in anthropometric parameters, as well as an increase of a metabolic parameter (HDL-cholesterol levels) and a reduction of another important metabolic parameter (triglycerides plasmatic levels).

In general terms, it was concluded that when prescribed in a rational way, taking the obese patient's physiopathologic conditions into consideration, and when associated to changes in diet and lifestyle, fluoxetine, sibutramine and metformin proved to be safe, well-tolerated and effective drugs in reducing some anthropometric and metabolic parameters in obese patients.

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