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Targeted weight reduction using Sibutramine.

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Summary (abstract)

Obesity is a serious chronic disease resulting from positive energy balance. Obesity is also an independent risk factor for the development of non-communicable widespread disorders. The endpoint of the trial was a targeted reduction of excessive body weight in 99 individuals with BMI over 30 or 27 kg/m^2 respectively. Three-month weight reduction therapy was based on the restriction of energy intake and pharmacotherapy by Sibutramine hydrochloride monohydrate (Sibutramine) 10 mg/person/day. Results: three-month targeted therapy resulted in statistically significant decrease of BMI, body weight, body fat and waist circumference. The reduction improved lipid profile and resulted in the decrease of systolic and diastolic blood pressure. Heart rate increased only insignificantly. Targeted reduction of excessive body weight using Sibutramine pharmacotherapy had a positive effect on anthropometric and biochemical characteristics without any adverse effect of nutrition in participating individuals.

Keywords:

Obesity, Sibutramine hydrochloride monohydrate, OMRON analyzer, energy intake, non-communicable widespread diseases, BMI,

Introduction

Obesity is defined as an increase of body weight associated with an increased share of body fat on the total body weight. Obesity should be regarded as a serious disorder and also an important risk factor for many other diseases. Obesity plays an important role in the ethiopathogenesis and development of non-communicable widespread diseases – diabetes mellitus, ischemic heart disease, and dyslipidaemia. Increased body weight and obesity result from positive energy balance. Energy balance is a difference between energy intake and output. If the energy intake in the form of food (particularly sugars and fats) exceeds actual needs (intake exceeds output), the excessive energy is stored in fat cells. The weight of fat tissue increases and so does the total body weights. The increase of the prevalence and incidence of excessive body weight and obesity is gradually accelerating worldwide since the second half of 20th century. This was documented by the results of many epidemiological studies performed during the 90's (14, 11, 15, 26).

Even last year Sibutramine hydrochloride monohydrate (sibutramine) titration 5 mg, 10mg or 15mg, was one of the most widely used drugs in the treatment of obesity for obese patients with an initial body mass index (BMI) ≥ 30 kg/m^2, or BMI ≥ 27 kg/m^2 with other risk factors (e.g., diabetes, high cholesterol, controlled high blood pressure). It was used under the trade names as prescription drug (Reductil, Meridia, Sibutrex, Sibutril, Lindaxa, Minimectil…) to 21.1.2010, when it has been suspended by Food and Drug Administration (FDA) and 3.3.2010 European Medicines Agency (EMA) on the basis of negative results of the study Sibutramine Cardiovascular Outcome Trial (SCOUT). The Committee for Medicinal Products for Human Use (CHMP) noted that the SCOUT study showed an increased risk of serious cardiovascular events (such as heart attack or stroke) in patients with known cardiovascular disease taking sibutramine.

This suspension will remain in force until the holder of registration does not provide data that will be sufficient to describe the group patients for whom the benefits of sibutramine administration clearly outweigh its risk. Today, the registration was renewed in the U.S., but only for obese patients, as defined in the original registration in 1997 (27, 28, 29).

Methods and selection of subjects

Targeted reduction of excessive body weight was performed on a selection of overweight and obese individuals. The total of 99 subjects with the average age of 40 ± 8 years were included. Basic study group was composed of 29 women (36 ± 6 years of age) and 70 men (41 ± 8 years of age). Only individuals comply-

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ing with the following selection criteria were included in the targeted weight reduction program: BMI ≥ 30 kg/m^2 or BMI ≥ 27 kg/m^2 and presence of other associated disorder (type 2 diabetes mellitus or hyperlipidaemia). Individuals that showed any contraindications for Sibutramine (1) therapy during the initial examination were excluded from the study. Our study was not affiliated or supported by any manufacturer.

Schedule of the three-month reduction diet:

V_0: *week -2 to 0*: entry examination, medical history, and determination of inclusion and exclusion criteria
V_1: *week 0*: anthropometry, blood sample collection, clinical examination (blood pressure, heart rate), and initiation of pharmacotherapy – first package of Sibutramine
V_2: *week 4*: anthropometry, clinical examination (blood pressure, heart rate), assessment of adverse effects, and second package of Sibutramine
V_3: *week 8*: anthropometry, clinical examination (blood pressure, heart rate), assessment of adverse effects, and third package of Sibutramine
V_4: *week 12*: final examination, anthropometry, blood sample collection, clinical examination (blood pressure, heart rate), and assessment of adverse effects

Methods – anthropometric characteristics were recorded under standard conditions in the morning on an empty stomach. These characteristics included current body weight and current height. Body mass index (BMI) was calculated based on these two values. Waist-hip ratio was determined using common tape measure. Assessment of body fat and its share on the total body weight was performed by bioelectrical impedance analysis using OMRON analyzer. Selected biochemical parameters – total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, glucose, and uric acid – were determined in the 0 and 12th week of the trial from venous blood samples collected from cubital vein in the morning on an empty stomach. Biochemical analysis was performed within 2 hours of sample collection in a specialized biochemical laboratory using HITACHI analyzer. The following parameters were assessed during examinations in V_0 – V_4: systolic blood pressure, diastolic blood pressure and heart rate. Measurements were performed in a sitting position after at least 20 minutes of rest. Targeted reduction weight therapy of individuals with excessive body weight and obesity was performed using Sibutramine, which was administered at the dose of 10mg/person/day. Pharmacotherapy was administered for the total of 3 months. All participants were advised during the entry examination to reduce daily energy intake by 400 – 600 Kcal when compared to objective long-term energy intake prior to the initiation of weight reduction therapy. Changes of dietary habits were monitored by the three-day consumption study. Statistical analysis of results was performed using basic statistical methods defining the dynamics of evaluated parameters – Access database system, paired Student t-test, ANOVA.

Results

Significant changes of selected anthropometric and biochemical characteristics were observed during the three-month targeted reduction of body weight in overweight and obese patients using Sibutramine pharmacotherapy. Table 1 summarizes the changes of body weight, BMI, absolute and relative body fat, waist and hip circumference in 70 male subjects. Statistically significant decrease of BMI ($p < 0.001$), statistically significant decrease of body fat ($p < 0.005$), statistically significant decrease of waist and hip circumference ($p < 0.001$) was demonstrated. Table 2 summarizes the changes of selected anthropometric characteristics in female subjects. Statistically significant decreases of BMI ($p < 0.05$), statistically significant decrease of body fat ($p < 0.001$), statistically significant decrease of waist ($p < 0.005$) and hip circumference ($p < 0.01$) were demonstrated. The dynamics of the changes of selected biochemical parameters between the entry and final examination (V_0 – V_4) for female and male subjects respectively is showed on Table 3 and 4. Statistical significance is also included. Data regarding the changes of systolic blood pressure, diastolic blood pressure and heart rate are shown in Table 5 for both male and female subjects.

Discussion

Obesity is a serious chronic disease that has significant impact on the health of an individual and decreases the average life expectancy. Obesity is also a serious socioeconomic problem, because it increases direct as well as indirect expenditure related to obesity treatment (2, 25). Complex therapy, including surgical treatment, is an effective approach to the reduction of excessive body weight from both individual and socioeconomic point of view (24). Complex treatment was used during the trial, including the reduction of daily energy intake by 400 – 600 Kcal in each of the subject. Alterations of eating habits were recommended within the scope of behavioural therapeutic approach – reduced consumption of fats and high-calorie diet, preference of low-calorie diet and increased consumption of dietary fiber. All 99 subjects of the study received Sibutramine at the dose of 10 mg/day/person for the period of 3 months in addition to complex weight reduction therapy. Primary endpoint of the trial was weight loss and reduction of body fat. Several studies have demonstrated positive correlation between weight reduction in obese patients and decreased risk of development of serious non-communicable widespread disorders (2, 22). Weight reduction decreases insulin resistance, improves glucose tolerance and normalizes lipid metabolism disorders (6, 17).

During the follow-up, we demonstrated weight loss of more than 10 % of the original body weight during the three-month pharmacotherapy in 15.25% of all subjects and decrease of more than 5 % and in 49.5% of all subjects – see Table 6. This table summarizes (separately for men and women) the results regard-

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ing the weight loss of 10% or 5% respectively from the original values. Following the three-month weight loss therapy, there were more female subject with weight loss of more than 10% as well as more than 5% of the original body weight – 17.2% and 58.6% respectively in comparison to male subjects – 14.3% and 45.7% respectively.

Authors of many short-term as well as long-term clinical randomized studies such as STORM demonstrated similar beneficial effect of Sibutramine on the decrease of body weight. The number of individuals with 10% as well as 5% decrease of body weight was higher than in the placebo group (12, 16). Sibutramine accentuates the decrease of body weight and helps to maintain this decrease if administered in the long run. Possible increase of body weight during Sibutramine therapy is not as frequent as for placebo (8, 26).

Waist circumference, typical primarily of central obesity, associated with higher amount of visceral fat, increases the risk of health impairment. Statistically significant decrease of the waist circumference in both men and women was demonstrated during the targeted three-month Sibutramine weight loss therapy – see Tables 1 and 2. Waist circumference is an independent risk factor that predicts the degree of obesity-related health impairment (18, 23). Positive correlation between the effect of Sibutramine during the weight reduction therapy and the waist circumference was reported by several clinical studies (9). Decrease of the visceral fat tissue lowers the risk of insulin resistance development and generally decreases the risk of health impairment. Decrease of the waist circumference also has a positive motivation effect on the maintenance of reduced body weight.

Unhealthy dietary habits with the preference of fat and sweets or high-calorie diet which is inadequate for the needs of the individual results not only in the development of obesity, but can also be the cause of lipid metabolism disorders. Obesity is very often associated with increased levels of atherogenic lipoproteins that accelerate the development of atherosclerosis. Restriction of energy and fat intake in the diet is the basic requirement for weight reduction and decrease of triglycerides, VLDL lipoproteins, total cholesterol as well as LDL cholesterol. Positive effect of weight reduction on the lipid profile was demonstrated in the male group – see Table 3. The decrease of total cholesterol, LDL cholesterol, triglycerides and increase of HDL cholesterol serum levels were recorded in the male group. Dujovne at al. demonstrated in his study of patients treated with Sibutramine the beneficial effect of weight reduction on the decrease of triglycerides levels and increase of HDL cholesterol levels. Increased body weight and obesity is often connected to the high-risk lipid profile – increased level of triglycerides and decreased level of HDL cholesterol. Sibutramine therapy has positive effect on the decrease of body weight and improves lipid profile. The above-mentioned changes decrease the risk of cardiovascular diseases (6, 21, 20, 22).

Our study demonstrated the decrease of systolic and diastolic blood pressure in both men and women following the three-month targeted weight reduction therapy. Statistically significant decrease of blood pressure was demonstrated in the female group. Heart rate increased insignificantly in all subjects (99 individuals) by the average of 1.4 heart beats per minute. The effects of Sibutramine on the blood pressure of both individuals with normal blood pressure and individuals with hypertension remain unclear. Some studies showed slight decrease of blood pressure in individuals treated with Sibutramine. On the contrary, some other studies showed slight increase of blood pressure (16, 19).

Selection of diet and preference of suitable food is very important for the overall success of complex weight reduction therapy and for the desirable weight loss. Sibutramine can be very helpful in the modification of dietary habits (3, 5, 10).

Conclusion

We performed targeted reduction of excessive weight loss on a selected group of 99 individuals. The endpoint was the reduction of body weight. Reduction of energy intake by 400 – 600 Kcal daily and pharmacotherapy by Sibutramine 10 mg/person/day were used as means of the weight reduction. Following the three-month therapy, weight loss, decrease of body fat, lower waist circumference, improved lipid profile and decreased of systolic as well as diastolic blood pressure were demonstrated. There was a statistically insignificant increase of heart rate during the study. Sibutramine therapy of obesity had no adverse effects that would result in the termination of therapy.

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