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Croatian Experience with Sibutramine in the Treatment of Obesity – Multicenter Prospective Study

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A B S T R A C T

Obesity is a chronic disease with a marked impact on health and the prevalence of obesity in Croatia is rapidly rising. Since obesity plays a significant role in the etiology of cardiovascular diseases, diabetes mellitus type 2 and of some cancers, it is an obvious target of public health activities. Weight-reducing drugs, like sibutramine, in combination with diet, exercise and behavioral changes have a role in the management of obesity. Sibutramine acts centrally as a serotonergic and noradrenergic reuptake inhibitor. It reduces body weight by enhancing satiety and stimulating thermogenesis. The aim of this multicenter prospective study was to evaluate the efficacy, tolerability and safety profile of sibutramine in the treatment of overweight patients in Croatia. Patients received 10 mg of sibutramine daily for 12 weeks. The main outcome measures were changes in body weight, BMI, waist and hip circumferences, laboratory assessments (serum triglicerida, cholesterol, glucose, HbA_{1c}), blood pressure and heart rate profile. Of 461 patients included (mean BMI = 35.81±6.48 kg/m^2, mean age = 43.65±10.90 years), 392 completed the study. Three months of sibutramine treatment lead to a significant reduction in body weight, BMI, waist and hip circumferences and improvement in metabolic parameters. Loss of over 5% of their initial body weight was found in 359 patients (91.58%), while 179 patients (45.66%) achieved weight loss over 10%. A decrease of both systolic (–3.39%) and diastolic (–3.75%) blood pressure was noted, while the pulse rate rose slightly (+0.13%). Adverse events were reported by 124 (26.90%) patients, but they precipitated only 17 (3.69%) withdrawals. Results of our study confirmed that sibutramine is an effective and safe weight-reducing drug.

Key words: *obesity, sibutramine, treatment, Croatia*

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Introduction

The World Health Organization has described obesity as a global epidemic that increases the risk of morbidity and mortality in a number of diseases, notably type 2 diabetes, dyslipidemia, hypertension and cardiovascular diseases. It also plays a role in the etiology of cancer, musculoskeletal disorders and mental health problems[1].

According to the epidemiological study called »The First Croatian Health Project« 79.2% of men and 49.9% of women in Croatia are overweight (BMI > 25 kg/ m^2) and 31.1% men and 15.2% women are obese (BMI > 30 kg/m^2)[2]. Despite the devastating health consequences of obesity, the effects of the preventive measures are still poor; moreover, doctors most often treat the complications rather than the underlying condition obesity itself.

Pharmacological therapy has been proposed as an adjunct to lifestyle modifications, reduced caloric intake and exercise in struggling with excessive body weight[3–5]. Sibutramine is an antiobesity drug that acts centrally as a serotonergic (5-HT) and noradrenergic (NA) reuptake inhibitor[6–8]. It reduces body weight by enhancing satiety and stimulating thermogenesis.

The aim of the present multicenter prospective study was to evaluate the efficacy, tolerability and safety profile of sibutramine in the treatment of overweight patients in Croatia.

Patients and Methods

A total of 461 obese adults (mean BMI = 35.81 ± 6.48 kg/m^2, mean age = 43.65 ± 10.90 years) were enrolled in the study. Patients were recruited from 47 different hospital and primary care sites in Croatia. Inclusion criteria were BMI = 30 kg/ m^2 or BMI = 27 kg/m^2 in patients with co-morbidities (diabetes mellitus type 2, dyslipidemia, hypertension). We enrolled 45 patients (11.48%) with diabetes mellitus: 12 patients (3.06%) were on metformin therapy and 2 patients (0.51%) on insulin.

Those with hepatic or renal dysfunction, a history of heart failure, ischaemic heart disease, stroke, transient ischaemic attacks, unstable hypertension and significant neurological or psychological illness were excluded.

Participants received 10 mg of sibutramine daily for 12 weeks. The dosage of sibutramine was increased to 15 mg after 4 weeks if weight loss during that period was less than 2 kg. Suggestions on diet and behavioral modifications were provided: the patients were suggested to make lifestyle interventions, to increase physical activity and to reduce the food intake (mildly reduced calorie diet). This behavior changes were not obligatory.

Efficacy assessments were changes in body weight, BMI, waist and hip circumferences, laboratory parameters (serum triglycerides, cholesterol, glucose, HbA_{1c}), blood pressure and heart rate profile. The statistical analysis was performed using the SPSS version 11 software package. Data were analyzed by paired Student's t test. p value < 0.05 was considered significant.

Results

Of the initial 461 patients, 392 completed the study (109 men, 283 women) and 69 withdrew (Figure 1). Adverse events precipitated 17 (3.69%) withdrawals. Only 4 (0.87%) patients specified a lack of efficacy as a cause of their withdrawal. Among those completing the study, there were 131 (33.42%) patients with hyper lipidemia, 122 (31.12%) patients with the history of hypertension and 45 (11.48%) patients with type 2 diabetes. Concomitant therapy was allowed (Figure 2).

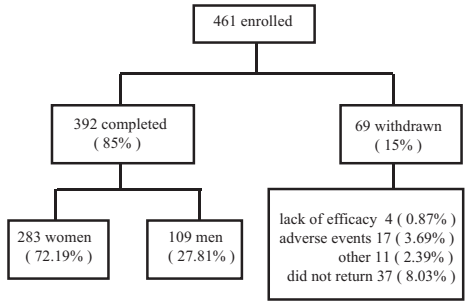

Fig. 1. Study participants.

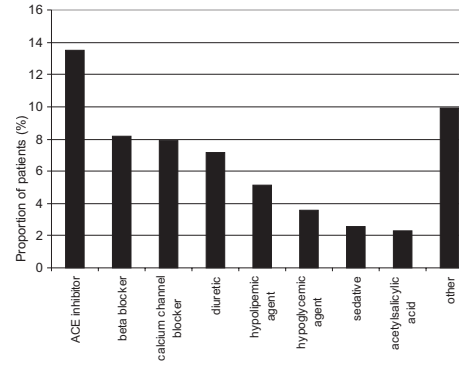

Fig. 2. Concomitant therapy for patients included in the study (N=392).

After 12 weeks of treatment with sibutramine, 359 (91.58%) patients lost > 5% of their initial body weight and 179 (45.66%) achieved a weight loss of > 10%. It was an evident and almost linear progressive weight loss throughout the study (Figure 3). Significant reduction in anthropometric parameters was observed; body weight was reduced for 10.00% ($p< 0.001$), BMI by 9.89% ($p<0.001$), waist circumference for 7.06% ($p<0.001$), and hip circumference by 6.37% ($p<0.001$) (Table 1).

All metabolic parameters representing cardiovascular risk factors submitted positive changes (Table 2). There were substantial decreases in concentrations of serum triglycerides (–19.49%, $p<0.001$), cholesterol (–9.46%, $p<0.001$), glucose

TABLE 1
CHANGES IN ANTHROPOMETRIC PARAMETERS FROM BASELINE TO THE END OF THE STUDY (N=392)

		Baseline	Week 12	Change (%)	p
Body weight (kg)	Men	117.97 ± 20.64	106.79 ± 19.59		
	Women	95.79 ± 16.84	85.97 ± 15.54		
	Overall	101.96 ± 20.52	91.76 ± 19.17	–10.00	<0.001
BMI (kg/m^2)	Men	36.99 ± 6.28	33.48 ± 6.04		
	Women	35.27 ± 6.50	31.65 ± 5.97		
	Overall	35.81 ± 6.48	32.27 ± 6.04	–9.89	<0.001
Waist circumference (cm)	Men	122.62 ± 16.21	113.73 ± 15.19		
	Women	104.58 ± 15.33	97.31 ± 14.69		
	Overall	109.55 ± 17.52	101.82 ± 16.59	–7.06	<0.001
Hip circumference (cm)	Men	121.49 ± 14.35	113.58 ± 12.83		
	Women	121.53 ± 13.96	113.85 ± 13.41		
	Overall	121.52 ± 14.05	114.78 ± 13.24	–6.37	<0.001

TABLE 2
CHANGES IN CARDIOVASCULAR INDICES FROM BASELINE TO THE END OF THE STUDY (N=392)

	Baseline	Week 12	Change	p
Triglicerida (mmol/L)	2.36 ± 1.97	1.90 ± 1.18	–19.49%	< 0.001
Cholesterol (mmol/L)	6.13 ± 1.36	5.55 ± 1.03	–9.46%	< 0.001
Glucose (mmol/L)	5.86 ± 1.78	5.51 ± 1.41	–5.97%	< 0.001
HbA_{1C} (%)	5.87 ± 1.38	5.57 ± 1.51	–5.11%	< 0.001
Systolic BP (mmHg)	135.50 ± 18.3	130.90 ± 13.1	–3.39%	< 0.001
Diastolic BP (mmHg)	85.38 ± 10.3	82.19 ± 8.0	–3.75%	< 0.001
Heart rate (beats/min)	76.82 ± 9.0	76.91 ± 8.4	+0.13%	0.08

(–5.97%, p<0.001) and HbA_{1c} (–5.11%, p= 0.002).

On average, from baseline to week 12, there was a significant decrease of systolic (–3.39%, p<0.001) and diastolic (–3.75%, p<0.001) blood pressure, while the pulse rate showed a slight but statistically insignificant increase (+0.13%, p= 0.08) (Table 2).

Adverse events were reported by 124 (26.90%) of patients. The most frequent were dry mouth, constipation and headache (Figure 4).

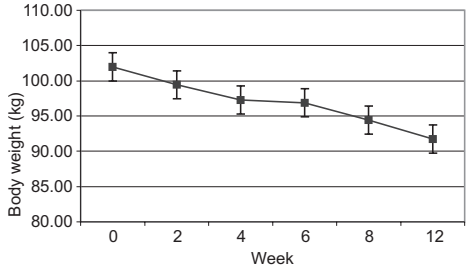

Fig. 3. Progressive weight loss throughout the study (N=392).

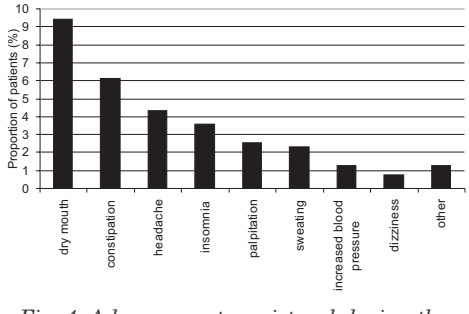

Fig. 4. Adverse events registered during the study (N=392).

Discussion

Obesity is a chronic disease with a marked impact on health[9]. Metabolic and genetic studies proved that obesity arises from an excess of energy intake compared to expenditure. Individuals inherit a set of genes controlling appetite and metabolism that are then acted upon by a wide variety of environmental factors such as food availability, level of physical activity, psychological and cultural factors[10,11].

A previous study on obesity carried out in Croatia provided information on national and regional patterns of body weight, nutritional status assessments and health risk factor correlates of obesity[2,12–15].

The prevalence of obesity in Croatia is rapidly rising. Half of all Croats presently die of cardiovascular diseases (50.3%), and additional 20% of neoplasm[2]. Having in mind that obesity plays a significant role in the etiology of cardiovascular diseases, diabetes mellitus type 2 and of some types of cancer; it is obvious that obesity

should be a target of public health activities in reducing morbidity and mortality. Primary preventive strategies should be focused on younger individuals because, as our data indicate, two thirds of patients become overweight before the age of 30. Another important point of weight management is the fact that non-pharmacological therapies fail on a larger scale. Consequently, weight-reducing drugs, like sibutramine, in combination with diet, exercise and behavioral changes have an important role in the management of obesity[16,17].

Results of our study confirmed that sibutramine is effective, safe, and that it reduces cardiovascular risk factors in obese patients. Three months treatment with sibutramine leads to significant reduction in body weight, BMI, waist and hip circumferences and an improvement of metabolic parameters.

Decrease in waist circumference is particularly important because it is well known that intra-abdominal fat accumulation is associated with a greater risk of cardiovascular diseases. Cutoffs indicating a significantly increased risk are waist circumference over 80 cm in women and over 94 cm in men[18].

A number of short-term trials have also demonstrated that sibutramine is able to promote significant weight loss[6,19–23]. Our study was designed very similarly to the German post marketing surveillance study on sibutramine in clinical practice. Within 12 weeks of treatment, 6,360 enrolled patients showed a mean body weight loss of 10.2%, BMI reduction of 10.7%, triglycerides decrease of 13.2%, cholesterol of 8.7%, glucose of 5.0% and HbA_{1C} of 4.9%, all corresponding to our results[24].

The STORM study (Sibutramine Trial of Obesity Reduction and Maintenance) is different from other weight loss trials because it showed not only the efficacy of sibutramine weight loss, but also indicated that sibutramine therapy could prevent weight regain for an additional period of 18 months among patients who lost over 5% of body weight in the first 6 months phase of the study. In the second phase, the patients were randomized to sibutramine or placebo; 43% of sibutramine treated patients maintained at least 80% of their weight loss in comparison to only 16% in the placebo group[25].

Reduction in triglyceride levels is also of great importance. An increase of only 1 mmol/L in triglyceride levels is associated with an increase of 76% of cardiovascular disease risk in women and a 31% increase in men[26].

In our study a significant decline in both, systolic and diastolic blood pressure was observed. Our results are in accordance with the mentioned German study[24]. However, in most of the other similar studies, a slight or significant increase in blood pressure was found[6,20,22,25,27–29].

A small increase of the mean pulse rate observed in our patients is in accordance with other sibutramine studies[6,19–23,25,27,30].

Furthermore, we observed a significant, weight-reduction associated improvement in glycemic control that confirmed the results of previous studies on sibutramine effectiveness in the treatment of obese type 2 diabetic patients[31–34].

Besides sibutramine, orlistat is another effective anti-obesity drug available for clinical use[35–38]. Orlistat acts peripherally blocking the dietary fat absorption. A number of studies have proven the impact of orlistat on weight loss. A recent study (XENDOS; XENical in the prevention of Diabetes in Obese Subjects) reported results showing that weight loss achieved with orlistat delays the development of diabetes over a 4-year period[39]. A comparison study on the efficacy of metformin, orlistat and sibutramine in obesity treatment found that sibutramine is

more effective than orlistat or metformin in weight reduction. Six months treatment with sibutramine, orlistat and metformin showed a significantly reduced BMI (–13.57%, –9.06% and –9.90% respectively)[40].

What can be expected in the future? Will overweight patients be treated with a sibutramine-permanant therapy, a sibutramine/orlistat combination or by using some new therapeutic strategy, remains to be seen? However, the long-term benefits of sibutramine therapy require further evaluation.

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HRVATSKO ISKUSTVO S KORIŠTENJEM SIBUTIRAMINA U LIJEČENJU PRETILOSTI – MULTICENTRIČNA PROSPEKTIVNA STUDIJA

S A Ž E T A K

Pretilost je kronična bolest, sa značajnim učinkom na zdravlje. Prevalencija pretilosti u Hrvatskoj vrtoglavo raste. Uzimajući u obzir da pretilost ima značajnu ulogu u etiologiji kardio-vaskularnih bolesti, dijabetes mellitusa tip 2 i nekih oblika raka, jasno je da pretilost treba biti cilj javno-zdravstvenih akcija, s ciljem smanjenja morbiditeta i mortaliteta u Hrvatskoj. Lijekovi koji snižavaju težinu, poput sibutiramina, u kombinaciji s dijetom, tjelovježbom i promjenama ponašanja imaju ulogu u tretmanu pretilosti. Sibutiramin ima centralno djelovanje kao serotoninergički i noradrenergički inhibitor ponovnog unosa. Tjelesnu težinu smanjuje poticanjem sitosti i pojačanjem termogeneze. Cilj ove multicentrične prospektivne studije bio je evaluacija efikasnosti, tolerancije i sigurnosti sibutiramina u liječenju pretilosti u Hrvatskoj. Pacijenti su tretirani s 10 mg sibutiramina dnevno, tijekom 12 tjedana. Glavni promatrani parametri bili su promjene tjelesne težine, BMI, opsega struka i bokova, laboratorijski nalazi (razina triglicerida u serumu, kolesterol, glukoza, te HbA_{1c}), krvni tlak i srčana frekvencija. Od 461 pacijenta uključenog u studiju (prosječni BMI = 35.81 ± 6.48 kg/m^2, prosječna starost = 43.65 ± 10,90 godina), 392 je završilo studiju. Tri mjeseca tretmana sibutiraminom rezultiralo je značajnom redukcijom tjelesne težine, BMI, opsega struka i bokova, te poboljšanje metaboličkih parametara. Gubitak više od 5% početne tjelesne težine je opserviran u 359 pacijenata (91,58%), dok je 179 pacijenata (45,66%) postiglo gubitak tjelesne težine veći od 10%. Uočeno je sniženje sistoličkog (–3,39%) i dijastoličkog (–3,75) tlaka, dok je srčana frekvencija blago porasla (+0,13%). Nuspojave su prijavila 124 pacijenta (26,90%), ali su uzrokovale samo 17 (3,69%) slučajeva ispadanja iz studije. Rezultati naše studije potvrđuju da je sibutiramin efikasan i siguran lijek za snižavanje tjelesne težine.