INFLUENCE OF SIBUTRAMINE, ORLISTAT AND *ISPAGHULA* IN REDUCING BODY WEIGHT AND TOTAL BODY FAT CONTENT IN OBESE INDIVIDUALS

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Background: The correlations between combined body fat parameters and risk factors of obesity explained a portion of the variation in the weight, BMI and waist circumference, the average number of categorical metabolic risk factors increases progressively with increasing total body fat content. There is currently no data available in which influence of drugs can be assessed on total body fat content. This was a non-randomized, prospective, open-label, parallel group study was conducted to compare the effectiveness of sibutramine, orlistat and ispahgula in reducing body weight and percentage of total body fat content in obese individuals. **Methods:** A nonrandomized, open label, prospective, intention to treat clinical trial was conducted from July 2008 to March 2009 in JPMC, Karachi, Pakistan. The study was based on three arms A (ispahgula), B (orlistat) and C (sibutramine) comprising 40 patients in each. The selection criteria has included patients from either sex with age 18 years or more with BMI ≥30 as obese with or without associated risk factors and BMI ≥27 <30 as over weight only if any significant risk factor is present. Compliance on diet chart and instruction for life style modification were assessed monthly. **Results:** The comparison of mean difference in percentage of total body fat content between the groups and within the groups at day 150 is (*p*-value) 0.029 and difference in body weight is (*p*-value) 0.042 which is statistically significant. **Conclusion:** Sibutramine is more effective than ispahgula and orlistat in reducing body weight and percentage of total body fat content in obese patients.

Keywords: Sibutramine, Orlistat, Ispahgula, body weight and obesity.

INTRODUCTION

Obesity is a growing health problem associated with chronic morbidity and premature mortality. It is now considered as a chronic disease that is reaching epidemic proportions because of combine sedentary life style with an ample supply of caloric rich foods.[1] Despite increased physicians and patient's awareness for obesity, the prevalence is increasing world wide.[2]

It is being reported that, during the year 2000, 65% of United States (US) adults were overweight (BMI ≥25 Kg/m^2), with 31% of adults classified as obese (BMI ≥30 Kg/m^2). In the past 20 years, there has been a disproportionate rise in severe obesity, with the BMI class ≥50 Kg/m^2 increasing almost 6-fold. Clinically most of the predictive power for men is contained in waist circumference, whereas for women, BMI and waist circumference were similarly predictive. Children in United States have shown sharp increases in bodyweight, with 16% classified as obese. The cost is high in morbidity and mortality, the expenditure had been $ 123 billion, plus $ 45 billion spent by the consumers on weight loss products and 6000 deaths occur per week from obesity complications.[3]

In Pakistan, obesity increases with advancing age, peaking at 45–64 years for both men and women in urban and rural settings and then decreasing after 65 years. The prevalence of obesity is higher in females than males regardless of age group and residence.[4] The obesity pandemic has important implications for Pakistan as well. In the National Health Survey of Pakistan (1990–1994), prevalence of obesity and increased BMI was more in urban than rural areas of Pakistan and it was related directly to the socio-economic status irrespective of residential area.[4]

WHO classified over weight according to BMI and percentage of total body fat content and evaluated a calculation for percentage of total body fat content, which is =1.2 (BMI) +0.23 (age) -10.8 (gender) -5.4 (Gender =1 for men and 0 for women). Women have 25 to 35 percent of total body fat content where as men have 15 to 25 percent of total body fat content.[5]

'Creeping obesity' results from a subtle imbalance – for example, a caloric excess of 30 kcal/day, represents a 1.5% mismatch of food intake to activity expenditure, will generate >200 lb weight gain during adult life. In the last few years US caloric consumption in men and women increased by 168 and 335 kcal/day, respectively.[6]

Sibutramine is a serotonin and norepinephrine reuptake inhibitor, which induces decrease in food intake and increases thermogenesis.[6, 7]

Orlistat is a lipase inhibitor, achieving 47% to 91% gastric lipase inhibition and a 51% to 82% pancreatic lipase inhibition.[7] It reduces fat absorption by

approximately one third and has no systemic action due to its minimal absorption.[8]

Psyllium, also referred to as ispaghula, is derived from the husk of the seeds of Plantago ovata. Psyllium contains a high level of soluble dietary fiber, and is the chief ingredient in many commonly used bulk laxatives.[9]

Aims of the study were to compare the effectiveness of sibutramine, orlistat and ispaghula in reducing body weight and percentage of total body fat content in obese individuals with intension to conducted clinical trial.

MATERIALS AND METHODS:

This was a nonrandomized, prospective, open-label, parallel group study carried out in the department of Pharmacology and Therapeutics, BMSI, in collaboration with Department of Medicine, JPMC, Karachi. The ethical committee of this institution has approved (NO. F.1-2/2008-BMSI/JPMC dated 8th June 2009) the study protocol. The sample size of 120 patients with 95% confidence interval and 99% confidence level was calculated by using a public service of Creative Research Systems tool and the level of precision was revalidated at the end of the study by considering the population at risk in Karachi.

The study was based on three groups A, B and C were ispaghula, orlistat and sibutramine respectively comprising 120 patients (40 patients in each group). The patients were assigned groups after assessing the risk and benefits of drug and with mutual understanding of both physician and the patients. The patients from either sex has been selected of age 18 years or more with BMI ≥30 as obese, BMI ≥27 <30 and as over weight if any significant risk factor (hyperlipidemia, diabetes, arthritis, sleep apnea etc) was present. The exclusion criteria included patients having history of malignant hypertension (Systolic and diastolic blood pressures greater than 220mmHg and 120mmHg, respectively), patients suffering from other gastrointestinal problems e.g. esophagitis, gastric carcinoma. Pregnant and lactating mothers, patient with known seizure disorders, patient with congestive heart failure, history of myocardial infarction and arrhythmias were also excluded.

The study was extended over a period of 150 days. Subjects were evaluated to determine eligibility for inclusion based on pre-specified criteria. During treatment period patients were selected to either group A, treated with ispaghula two table spoon three times daily, group B was provided orlistat 120 mg three times daily and Group C were given sibutramine 15mg once daily for a period of 150 days.

The safety and tolerability of Ispaghula, Orlistat and sibutramine were assessed by monitoring adverse events by history and general physical examination at each visit.

The limitations of the study were that patient were nonrandomized and it was an open trial and they had different risk factors like diabetes, arthritis and few patients did not have any concomitant illness. The base line demographic distribution was similar in all three groups except 5 kilograms mean difference between group A and B but the difference is not significant (*p*-value 0.724 with 95% C.I. is -5.4–10.6). There were five patients who lost follow-up in orlistat group as compared to four in ispaghula and one in sibutramine.

All the values are taken as mean and ±SEM. The primary efficacy measurement was the mean change in the monthly body weight and percentage of total body fat content from baseline to end point. The SPSS 16.0 was used to analyze the data. The dependent variables were body weight and percentage of total body fat content Independent variables were age, height and gender with factors for one way ANOVA were values and parameter at day 0 and day 150 on the basis of groups A, B and C. The Tukey Post Hoc test was used to examine the statistical difference within the groups and among the groups.

RESULTS

A total of 120 patients were treated for a period of 150 days out of which 63.3% were females and 36.7% were male with 27, 24 and 25 numbers of female in groups A, B & C respectively. The mean age was 41.32± 0.97 years. The mean BMI was 36.88±0.56 at day zero of the study. 64% of the patients have associated risk factors like diabetes, hypertension, ischemic heart disease, arthritis, dyslipidemia, sleep apnea etc. The average height was 1.61±0.013 meters and weight was 95.47±1.54 kilograms with total body fat content 39.16±0.92 at the beginning of the study.

The mean percentage of total body fat content at day zero was similar in all three groups while Orlistat is slightly higher with a percentage of 40.73±1.87 as compared to 38.59±1.79 and 38.15±0.97 in Ispaghula and Sibutramine respectively. The body weight was 92.5±2.06, 98.38±2.49 and 95.54±3.27 in groups A, B and C respectively.

The mean difference of the percentage of total body fat content was not significant at day zero of the study. The difference between group A and B is 2.14, A and C is 0.44 and B and C is 2.58 with a *p*-value of 0.61, 0.98 and 0.49 respectively which is not significant.

The mean weight and total body fat content declined in all the three groups as compare to the values at day zero. The mean weight of group A, B and C are 87.87±1.94, 90.46±2.37 and 82.04±2.77 respectively and mean total body fat content was 36.61±1.73, 36.85±1.66 and 31.94 ±0.713 in group A,B and C respectively.

The mean difference of the percentage of total body fat content between group A and B at day 150 is 0.238, A and C is 4.664 and B and C is 4.90 with a P- value of 0.993, 0.063 and 0.047 respectively. Hence there is not significant difference in ispaghula in reducing body fat content as compare to orlistat but sibutramine has reduced percentage of body fat content significantly as compared to groups A and B.

The mean difference in the body weight at day 150 between group A and B is 2.857, and C is 5.837 and B and C is 8.425 with a *p*-value of 0.724, 0.199 and 0.037 respectively. However the mean change in weight from day zero to day 150 in group A is 4.7 (5.1%) in group B is 7.9 (8.0%) and in group C is 13.5 (14.1%).

The mean difference in percentage of total body fat content between the groups and within the groups is not significant at day zero with a *p*-value 0.479 where as at day 150 it is 0.029 which is significant.

The mean difference in body weight between the groups and among the group is not significant at day zero with a *p*-value 0.299 however at day 150 it is 0.042 which is significant.

Patients reported adverse events in the orlistat treated group which were all related to the gastrointestinal tract. The most commonly reported events were flatulence with discharge (10%), oily stool with increased defecation (14%), feeling of fullness in the stomach (8%) and constipation (2%). The sibutramine treated group has shown slight increase in systolic blood pressure (30%), diastolic blood pressure (20%), increase pulse rate (25%), insomnia, dry mouth and constipation (10%) and (0.4%) chest pain. Patients on ispaghula have complained of abdominal distention and fullness (15%) and increase frequency of defecation (10%).

DISCUSSION

All the three drugs were effective in loosing weight but sibutramine was more effective in losing weight and total body fat content as compared to ispaghula and orlistat. When we compared sibutramine against orlistat and Ispaghula, sibutramine was found to be superior in reducing weight against orlistat and relatively less significant against Ispaghula although patients with orlistat has reduced (7.9 Kg) 8.0% as compared to ispaghula (4.7 Kg) 5.1% weight loss from base line. At the beginning of this study ispaghula group had 5% less weight as compared to orlistat group although the difference was not significant statistically (*p*-value 0.724 with 95% CI. is -5.4–10.6) but along with a limitation of more dropout in the orlistat group were possible confounders in our study. The results for orlistat were similar to results shown by Feigenbaun and collegue[11] which has shown 7.8 Kg reduction in weight as compared to 7.9 kg in our study.

In a clinical trial, sibutramine showed a statistical improvement in amount of weight loss versus placebo[5]. It limits decline of metabolic rate that typically accompanies weight loss. However, this agent was contraindicated in patients with known seizure disorders, high blood pressure, congestive heart failure (CHF) a history of myocardial infarction and arrhythmias.[5,12] In Canada reports of 28 adverse events (no deaths) in patients using sibutramine were received between December 2000 and February 2002.[13,14] However in our study patients have shown increase in systolic and diastolic blood pressure, increased pulse rate, insomnia, dry mouth, constipation and mild chest pain.

Table-1: Mean difference in % of TBFC and Body weight among the groups at day zero and 150

(I) group (day 0)	(J) group (day 0)	Day 0 Mean Difference (I-J)	*p*-value	95% Confidence Interval		Day 150 Mean Difference (I-J)	*p*-value	95% Confidence Interval	
				Lower Bound	Upper Bound			Lower Bound	Upper Bound
Ispaghol %TBFC	Orlistat	-2.13652	0.614	-7.5163	3.2432	-0.23806	0.993	-5.0938	4.6176
	Subitramine	0.44363	0.979	-4.9361	5.8234	4.66403	0.063	-0.1917	9.5197
Orlistat %TBFC	Ispaghol	2.13652	0.614	-3.2432	7.5163	0.23806	0.993	-4.6176	5.0938
	Subitramine	2.58015	0.492	-2.7996	7.9599	4.90209*	0.047	0.0464	9.7578
Subitramine %TBFC	Ispaghol	-0.44363	0.979	-5.8234	4.9361	-4.66403	0.063	-9.5197	.1917
	Orlistat	-2.58015	0.492	-7.9599	2.7996	-4.90209*	0.047	-9.7578	-.0464
Ispaghol WEIGHT	Orlistat	-5.875	0.266	-14.80	3.05	-2.58750	0.724	-10.6049	5.4299
	Subitramine	-3.037	0.699	-11.97	5.89	5.83750	0.199	-2.1799	13.8549
Orlistat WEIGHT	Ispaghol	5.875	0.266	-3.05	14.80	2.58750	0.724	-5.4299	10.6049
	Subitramine	2.838	0.732	-6.09	11.77	8.42500*	0.037	0.4076	16.4424
Subitramine WEIGHT	Ispaghol	3.037	0.699	-5.89	11.97	-5.83750	0.199	-13.8549	2.1799
	Orlistat	-2.838	0.732	-11.77	6.09	-8.42500*	0.037	-16.4424	-0.4076

TBFC= Total Body Fat Content

Table-2: Mean difference in TBFC and body weight within the groups and among the group at day 0 and 150

	Sum of Squares	df	Mean Square	F	*p*-value
Between Groups %TBFC Day 0	152.25	2	76.125	0.74	0.479
Within Groups %TBFC Day 0	12017.322	117	102.712		
Between Groups weight Day 0	690.579	2	345.29	1.221	0.299
Within Groups weight Day 0	33097.069	117	282.88		
Between Groups TBFC Day 150	611.204	2	305.602	3.652	0.029
Within Groups TBFC Day 150	9790.217	117	83.677		
Between Groups Weight day 150	1490.029	2	745.015	3.266	0.042
Within Groups weight Day 150	26690.292	117	228.122		

df=Degree of freedom; F= F test; TBFC= Total Body Fat Content

It was reported by Feigenbaun that adverse effects of orlistat related to gastrointestinal tract were flatulence with discharge (9.2%), fatty and oily stool with increased defecation (9.2%), feeling of fullness in the stomach (4.6%), and constipation (1.7%).[11] These side effects were similar to side effects observed in our study.

The reviewed evidence seems to show that ispaghula may improve blood sugar, lipid levels and decrease body fat content, which can be related to obesity in some individuals. However, further studies are needed to clarify its effects and the mechanisms Early research shows that dietary psyllium and chitosan supplementation may help to increase the excretion of fat in the stool. This could be underline mechanism of weight loss along with decrease in appetite involved to be associated with psyllium use in adults.[9]

There is inadequate data available of our population regarding the mapping of demographic distribution and prevalence of obesity. It is important that work should be done with regard to tackling this health issue, which is of significant consequence in the long term. Emphasis should be on promoting low intensity long duration physical activity that can be conveniently incorporated into daily life along with diet pills if required and more studies should be conducted in our population so as to establish guidelines on nutrition, weight status and need of medicines for reduction in weight after assessing the risk and benefits of using pharmacological agents. It is suggested that all weight reducing agents whether pharmacological or non pharmacological should only be allowed to market if the label shows the ingredients and chemical composition of these agents.

CONCLUSION

Ispaghula, orlistat and sibutramine all reduce weight and percentage of total body fat content but only sibutramine reduces weight more significantly when we compare the drugs among the groups.

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