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COMPARISON OF EFFICACY AND SAFETY OF RIMONABANT WITH ORLISTAT IN OBESE AND OVERWEIGHT PATIENTS

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ABSTRACT

Introduction- Rapidly rising prevalence of obesity is alarming. Obesity predisposes to co-morbidities like hypertension, Type 2 Diabetes Mellitus, dyslipidemias thus substantially rising health care expenditure. Lifestyle modifications alone have very limited success; necessitate the addition of pharmacotherapy to it.
Objective- Present study was carried out to compare efficacy and safety of new drug Rimonabant with Orlistat
Methodology- 90 obese (BMI>30) or overweight (BMI >27) with co-morbidity patients after initial screening for common endocrinological causes were randomized into either Rimonabant 20mg once a day or Orlistat 120mg three times a day or Placebo group. Weight, waist circumference, total cholesterol, triglycerides, HDL, LDL were recorded at baseline and then at 2^{nd},4^{th} & 6^{th} month. ADR reported by patients were recorded. For safety evaluation various hematological & biochemical parameters were assessed. Originally planned duration of 12 months was reduced to 6 months after Rimonabant was banned.
Results- Compared to placebo Rimonabant caused significant reduction in weight (5.4±0.5 kg), waist circumference (4.7±0.5 cm), triglyceride (8.6±3.2 %), and increase in HDL (18±4.1 %). Orlistat caused significant reduction in weight (4.9±0.8 kg), waist circumference (4.0 ± 0.6 cm), total cholesterol (6.13±1.4 %), LDL (7.93±1.3 %). Orlistat caused GIT side effects while Rimonabant caused nausea, URTI, diarrhea.
Conclusion- Rimonabant has a similar weight loss efficacy to Orlistat but different effect on lipid profile with a substantially low cost 5-8 Rs/day Vs 120/day for Orlistat. Rimonabant was banned because of severe psychiatric side effects.

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KEY WORDS

Obesity, Overweight, Rimonabant, Orlistat, antiobesity drugs

INTRODUCTION

Survival requires continues provision of energy to maintain homeostasis even when the food supply is intermittent. Evolution has given us a mechanism for storing any excess latent energy in foodstuffs in adipose tissue as energy dense triglycerides, which can be easily mobilized when food in absent or less abundant. This mechanism was an obvious asset to our hunter gatherer ancestors.[1,2]

However in many societies a combination of sedentary lifestyle, genetic susceptibility, cultural influences and easy access to calorie dense foods is leading to a global epidemic of obesity or *globesity*

Obesity is a state of excess adipose tissue mass. Approximate prevalence is 30 % and is rapidly rising. Obesity leads to increase in morbidity rather than mortality; it increases the prevalence of co morbidities like hypertension, dyslipidemias, type 2 Diabetes Mellitus, endocrinological abnormalities and higher mortality from few cancers. [2]

Initial measures taken to combat obesity like dietary restriction and exercise are usually met with short term success and are often inadequate alone. That's why for treatment of obesity there is need for pharmacotherapy as adjunct to lifestyle changes.

Most older and new antiobesity drugs act on CNS to suppress appetite and reduce food intake. Most of the older drugs like amphetamine, phentermine. fenfluramine have been banned because of severe adverse effects. Sibutramine is one of the only two drugs available today has cardiovascular effects like increase in heart rate and blood pressure making it unsuitable for large proportion of obese patients with CVS ailment. [4]

Orlistat is hydrogenated derivative of lipstatin. It inhibits the gastric and pancreatic lipase thereby preventing breakdown of dietary fat into fatty acids thus reducing fat absorption by 30%.[4]

Rimonabant a first in its class drug in novel category of cannabinoid receptor blockers. It is antagonist at CB1 receptors in CNS involved in food regulation [5]

Objective

The present study aimed to compare the efficacy and safety of Rimonabant with Orlistat, in combination with dietary advice as therapy for weight loss over 6 months in obese and overweight patients.

MATERIAL AND METHODS

Patients-

90 patients with BMI > 30 or BMI >27 with co morbidities like hypertension or untreated dyslipidemia were enrolled in study after informed consent

Exclusion criteria's applied were obesity of endocrinal origin, use of medications that can alter body weight, unstable body weight in last 3 months, clinically significant CVS, Respiratory or hepatobiliary disorder, past or present psychiatric illness, chronic diarrhea

Design-

This study was randomized single blind parallel group study carried out at Out Patient Department of Dr.Patwardhans Endocrinology Hospital over the period of 6 months. Study protocol was approved by Institutional Ethical Committee. Initial Planned duration of 12

months stretching from July 2008 to June 2009 had to be reduced to 6 months after Rimonabant was banned in Dec 20008

90 patients meeting the inclusion and exclusion criteria were randomized into any of the three group's viz. Placebo, Orlistat or Rimonabant.

In Orlistat group patients were advised to take 1 tablet of Orlistat 120 mg with each major meal making it three tablets a day, Rimonabant group patients were asked to take 1 tablet of 20 mg a day. Placebo group was given placebo once a day. Compliance of medication was checked by pill count.

Irrespective of group allotted all the patients were educated about the importance of lifestyle changes including healthy dietary habits and exercise in weight reduction and maintenance. Patients were given information about nutritional value of various foods and few simple exercises for decreasing and maintaining near normal body weight. Their compliance for life style change advice was checked through verbal questions at each visit.

Parameters under consideration were checked at baseline to make sure that their values were similar before starting the drugs. In the study patients were asked to do a follow up visit after 2^{nd}, 4^{th} and 6^{th} month during which all the anthropological measurements and laboratory analysis was done.

All the principles of declaration of Helsinki were followed.

Efficacy parameters –

Primary efficacy parameter under consideration was body weight (in kg) measured on calibrated electronic weighing scale. Other parameters included waist circumference measured in cm. Blood cholesterol, LDL, HDL and triglyceride levels using standard laboratory procedures. Blood sugar level and Blood Pressure were also measured at every visit.

Safety parameters –

Safety evaluation of the drug was done by carrying out routine hematological and biochemical investigations at baseline and every follow up.

All the adverse reactions reported by patients were recorded with severity as and when reported by patients.

Analysis-

Unpaired t test was used to compare active treatment group with placebo one at a time.

RESULTS

Out of 30 patients in each group, 28 in placebo, 26 in Orlistat group and 26 in Rimonabant completed the trial. Only completer's data was used in calculations.

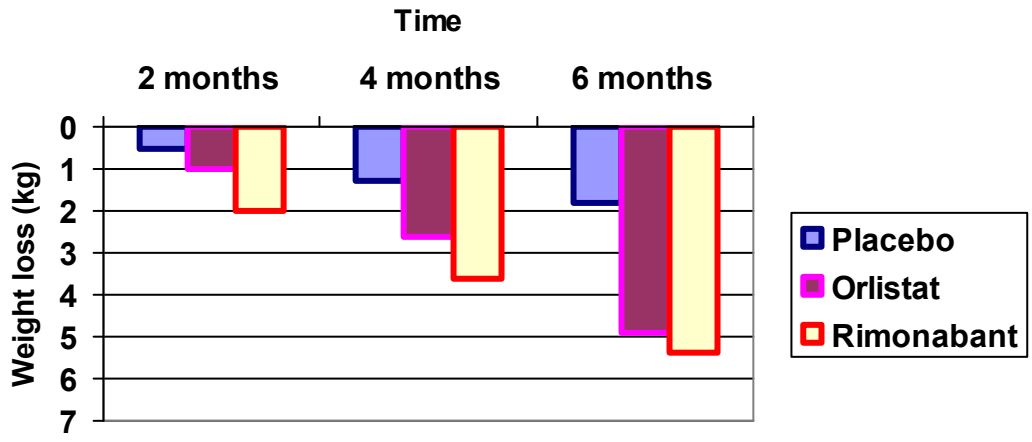
Table 1
Patient's characteristic at baseline

	Placebo	Orlistat	Rimonabant	P value
Total Number	30	30	30	<0.05
Male	9	11	10	<0.05
Female	21	19	20	<0.05
Weight (kg)	95.0 ± 15	94.2± 13	93.3±14	<0.05
BMI	34.0± 3.5	34±3.5	33.9±3.3	<0.05

Table 2
Patient's characteristic at the end of study

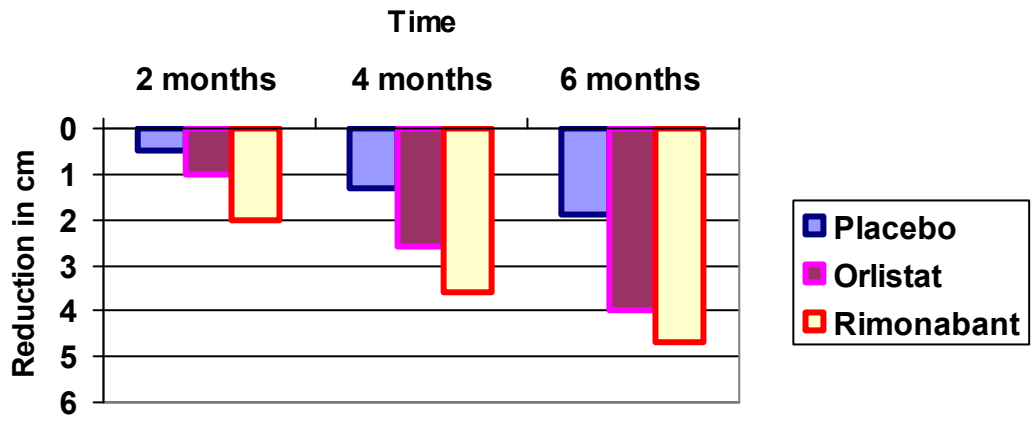
	Placebo	Orlistat	Rimonabant
Weight loss (kg)	1.8±0.4	4.9±0.8	5.4±0.5
Waist circumference reduction (cm)	1.9±0.4	4.0±0.6	4.7±0.5
Total cholesterol reduction (%)	1.2±2.0	6.1±1.8	1.6±2.1
Total triglyceride reduction (%)	2.1±0.6	2.8±1.8	8.6±3.2
LDL reduction (%)	0.8±1.1	7.9±1.8	1.6±0.4
HDL increase (%)	10±3.2	4.2±1.1	18±4.1

Graph1. Effect of drugs on body weight



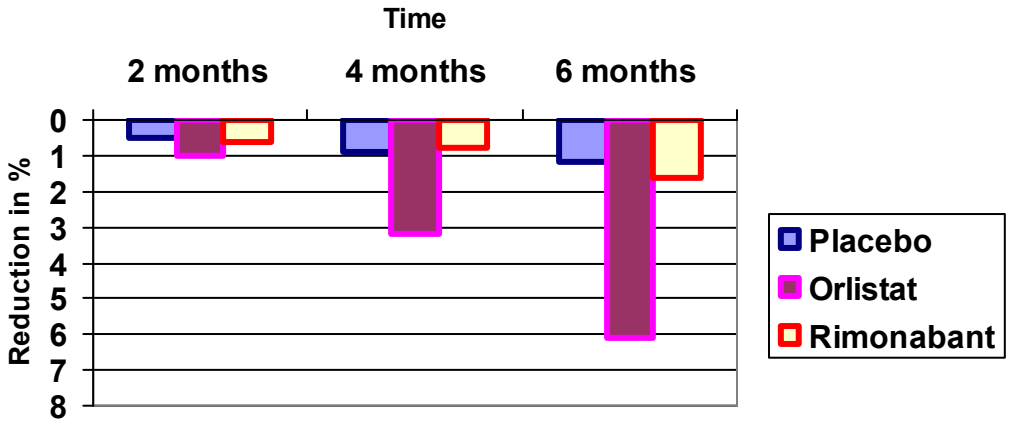
At the end of the study average loss of initial body weight in placebo group was 1.8±0.4 kg, 4.9±0.8 kg in Orlistat group, 5.4±0.5 kg in Rimonabant treated patients. Weight loss caused by Rimonabant and Orlistat was statistically significant compared to placebo

Graph 2. Effect of drugs on waist circumference



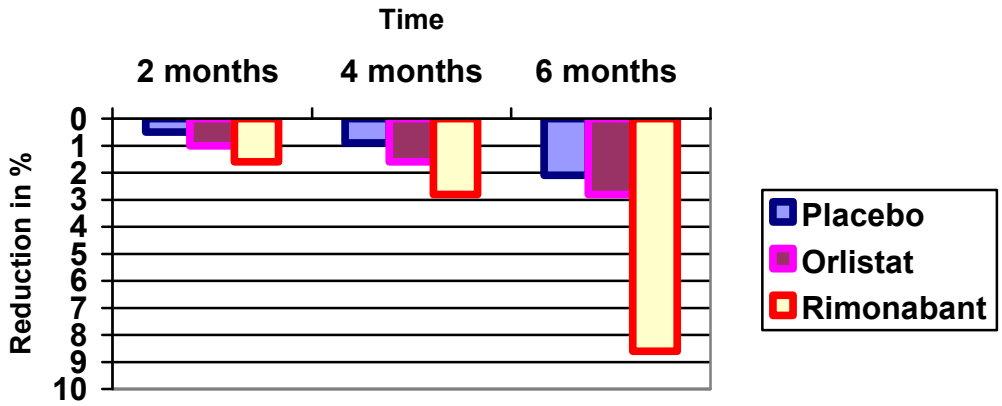
At the end of the study average reduction in waist circumference in placebo group was 1.9±0.4 cm, 4.0±0.6 cm in Orlistat group, 4.7±0.5 cm in Rimonabant treated patients. Reduction in waist circumference caused by Rimonabant and Orlistat was statistically significant compared to placebo

Graph 3. Effect of drugs on Cholesterol level



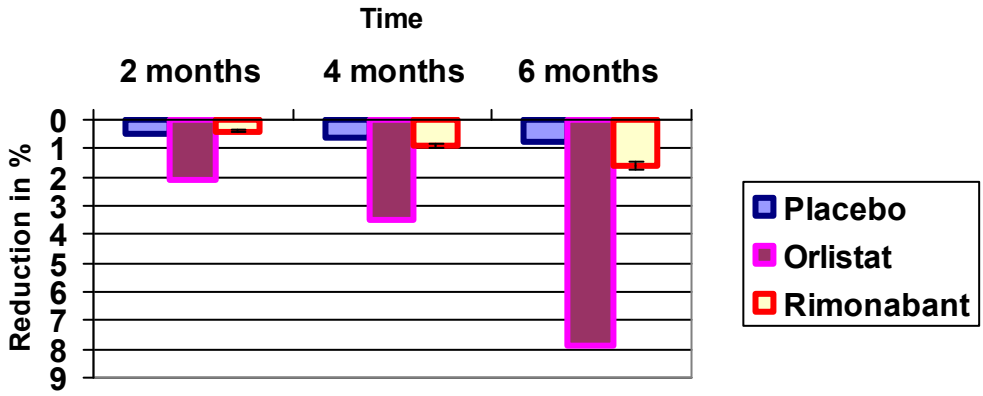
At the end of the study average reduction in cholesterol level in placebo group was 1.2±2.0 %, 6.1±1.8 % in Orlistat group, 1.6±2.1 % in Rimonabant treated patients. Reduction in cholesterol level caused by Orlistat was statistically significant compared to placebo

Graph 4. Effect of drugs on triglyceride level



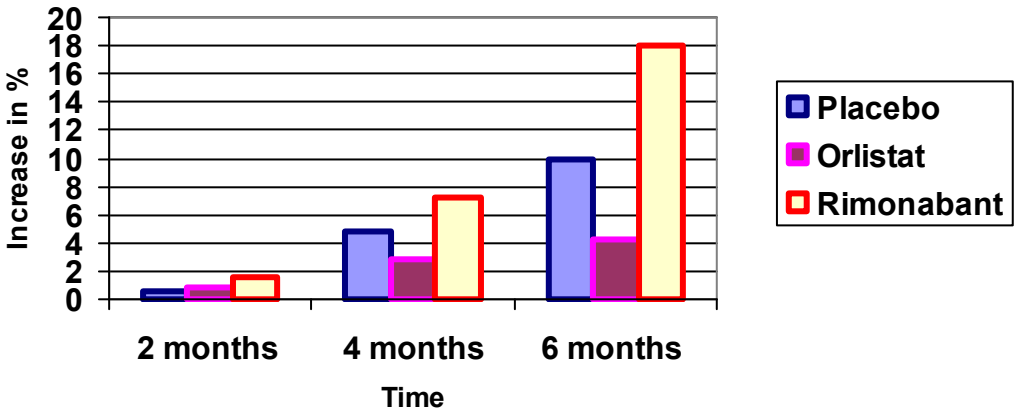
At the end of the study average reduction in triglyceride level in placebo group was 2.1±0.6 %, 2.8±1.8 % in Orlistat group, 8.6 % in Rimonabant treated patients. Reduction in triglyceride level caused by Rimonabant was statistically significant compared to placebo

Graph 5. Effect of drugs on LDL level



At the end of the study average reduction in LDL level in placebo group was 0.8 %, 7.9 % in Orlistat group, and 1.6±0.4 % in Rimonabant treated patients. Reduction in triglyceride level caused by Orlistat was statistically significant compared to placebo

Graph 6. Effect of drugs on HDL level



At the end of the study average increase HDL level in placebo group was 10±3.2 %, 4.2±1.1 % in Orlistat group, 18±4.1 % in Rimonabant treated patients. Increase in HDL level caused by Rimonabant was statistically significant compared to placebo

Adverse events

Overall incidence of ADR was more in active treatment group than placebo group

Almost 65% of patients in Orlistat group had experienced at least one GI adverse event; Most common being oily stool, oily spotting and fecal urgency. Out of the 4 patients who withdrew from Orlistat group 2 withdrew because of sever side effects while 2 patients were lost to follow up.

Most common ADR seen in Rimonabant group were nausea, URTI, Diarrhea. Out of the 4 patients who withdrew from Rimonabant group 1 withdrew because of depression (diagnosed by general physician) while rest 3 patients were lost to follow up.

In placebo group 2 patients withdrew because they were unsatisfied with the extent of weight loss.

All the findings of the routine hematological and biochemical investigations were within normal limits for all the study group with minor variations.

DISCUSSION

In this study, efficacy and safety of a new drug Rimonabant was compared with Orlistat which currently leads the anti-obesity drug market over the period of 6 months.

It was observed that both Rimonabant and Orlistat caused weight loss significantly more than placebo but was similar to each other.

Waist circumference is marker of abdominal obesity which is a major independent risk factor for CVS disorders and a primary target for treatment of metabolic syndrome. [2]

Both the treatment groups had lead to reduction in waist circumference significantly greater than placebo group even though there was no significant difference between the extents of waist circumference reduction caused by both the treatment groups.

Even though weight reduction was similar in both the treatment groups Rimonabant and Orlistat have different effects on the lipid profile.

Rimonabant caused significant reduction in triglycerides levels with significant increase in HDL levels as compared to placebo.

Orlistat caused significant reduction in total Cholesterol levels and LDL levels as compared to placebo.

While in placebo group all the beneficial changes in weight and lipid profile can be attributed to the healthy lifestyle changes (Diet and Exercise) adopted by the patients.

Comparing with the previous studies on Orlistat this study had similar results except for the higher compliance in the present study. In literature Orlistat has been shown to reduce incidence of development of diabetes mellitus in prediabetic,and slightly reduce B.P. [3]

Previous studies on Rimonabant have results similar to present study and in addition it has been shown to decrease the prevalence of metabolic syndrome, making LDL particles less atherogenic and slight reduction of Blood Pressure in Hypertensive. As compared to the literature on Rimonabant the present study had significantly lesser incidence of psychiatric side effects, which could be because of exclusion of patients with past or present history of any psychiatric illness or even patients living stressful life. [5,6,7,]

The effect of Rimonabant and Orlistat on blood sugar level and blood pressure was not found to be significant (results not shown) and not evaluated as they possibly got confounded by associated diabetes mellitus or Hypertension and its treatment.

One important finding this study tries to put forward is the cost of treatment. Orlistat with standard dose of 120 mg t.i.d. cost about 120 Rs/day. Rimonabant which has similar weight reduction efficacy comes at a significantly lesser cost i.e. 5-8 Rs/day. But the side effects of both the drug are incomparable.

The GIT side effects caused by Orlistat even though socially embarrassing are still acceptable as compared to possible psychiatric side effects with Rimonabant like depression anxiety and very rarely suicidal tendencies. So the advantage of low cost of Rimonabant should be weighed against the disadvantage of possible psychiatric reactions.

Beneficial changes in placebo group reemphasize the important role of life style changes in weight reduction and maintenance. It goes without saying that the efficacy these two drugs or for that matter any anti obesity drug has shown till date would be significantly reduced in the absence of associated life style modification.

Limitations

Present study was planned for 12 months but had to reduce to 6 months after Rimonabant was banned for concerns over its neuropsychiatric side effects.

As seen in previous weight reduction trials that there are two distinct phases, the initial phase of 8-9 months leading to significant weight loss then in second phase this weight stabilizes in spite of continuing the same treatment. As present study was only of 6 months it well may be a part of initial phase of rapid weight loss which might stabilize afterwards

CONCLUSION

Rimonabant is equally efficacious as its older counterpart Orlistat that too at low cost but with possibility of severe neuropsychiatric side effects which led to its withdrawal. But with the variety of effects it has it could have been a good drug for metabolic syndrome. The major drawback of Orlistat is its high price.

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