Study of the Efficacy of Orlistat and Sibutramine in Combination for the Treatment of Obesity

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A. Rationale

Approximately 97 million Americans, more than 50 % of the adult population, have been deemed overweight or obese.[1] In fact, obesity is considered one of the most preventable causes of death in the United States-Obesity, defined as a body mass index (BNH) 2:30, is associated with numerous medical conditions, such as atherosclerotic heart disease, type 11 diabetes, dyslipidemia, hypertension, osteoarthritis, and sleep apnea. Evidence to date suggests that weight loss as little a 5-10% can significantly improve obesity related conditions. [2,1,4] The pharmaceutical industry has recently developed two oral agents, sibutramine (FDA approved) and orlistat (awaiting FDA approval), to assist in the battle for weight loss. This study proposes to evaluate the efficacy of combination of these anti-obesity agents compare to use another agent alone.

B. Study Design

Suggested here is a randomized, placebo-controlled, double-blind study of the combined oral use of sibutramine and orlistat, compared to orlistat, and sibutramine alone during a 24 week period. Approximately 225 individuals between the ages of 18-65, with calculated BX11 _> 30 will be needed for the study. Eligible subjects will participate in a 2 week run -in period during which they will be prescribed one sibutramine-like placebo (A) pill daily, and one orlistat-like placebo (B) pill three times a day with meals. They will be instructed to follow a 1500 calorie diet, with less than 30 % calories derived from fat, and an exercise program of walking or similar physical activity for 30 minutes 3 days/week. Individuals who demonstrate 75% compliance with placebo use will be included in the study. Eligible individuals will be randomized into three groups, by a computer generated program factoring in sex and ethnicity (Caucasian, African-American, Hispanic, or Other), until 75 subjects are in each group*.

At the end of the run in period, Group I will be switched to a regimen of sibutramine 10 mg daily plus orlistat 120 mg three times a day. Group II will receive sibutramine 10 mg daily plus placebo B three times daily. Group III will receive placebo A once daily, plus orlistat 120 ing three times daily. During the course and at the end of the 24 week study period, the absolute weight lost (kg), the percentage of initial body weight lost, and the change in BNH will be assessed. This should allow for comparisons in efficacy in terms of weight lost between groups I and 11, and groups I and 1111. Analysis will be based on intention to treat.

*The number of study participants per group was determined by using the calculation: n = 16 (SD A)2 + 2. In a previous obesity study, the standard deviation (SD) of weight loss was 7.5 kg.5 It is estimated that combination of drug use will lead to an additional 3.5 kg loss (A= 3.5). Therefore, approximately 75 subjects are needed in each study arm to provide a power of 80%, and a significance level of 5%.

C. Study Procedures

The initial encounter with patients will include discussion of study purpose, design, drugs, and possible risks and benefits of study participation. Prospective subjects will then undergo a general physical, measurements of blood pressure, height, weight, and calculation of the BNII for research purposes. Additional laboratory data, such as an EKG, and blood tests (including CBC, Chem 7, hepatic profile, PT, and vitamin A, D, and E levels) will be obtained for clinical management purposes.

After the initia 2 week run-in period, patient encounters will be scheduled every 2 weeks for the first two months. Encounters will then occur every I month until the completion of the 24 week study period. Each visit will serve to record measurements of height, weight, BN11, to review 24 hour food diaries, and to obtain physical activity questionnaire information. Repeat analysis of fat soluble vitan-fin levels in the blood will occur at month 3 and at the termination of study period. The food diaries, vitamin levels, and physical activity data are required as part of a subject's clinical management.

The anticipated duration of each subject's participation is 26 weeks. The likely duration of the entire study is I year.

D. Study Drugs

a. Sibutramine (Meridia)

Sibutramine is an orally administered product of Knoll Pharmaceuticals that is FDA approved for use in obesity management. It is a serotonin and norepinephrine reuptake inhibitor that acts centrally by increasing satiety and possibly energy expenditure, while decreasing appetite. Unlike previous appetite suppressants, Sibutramine does not have abuse potential.

In one 24 week study of drug efficacy, doses of sibutramine 10 mg daily were shown to elicit a mean weight loss of 7.3 kg (7.75% bodyweight) in men and 6.19 kg (6.9 1 % bodyweight) in women. This was compared to a mean 0.24 kg weight gain in male placebo recipients, and a mean 0.75kg (0.77%) weight loss in female placebo.

recipients. Another 24 week dose ranging study of 683 patients showed a loss of 6. 1% of initial body weight in subjects receiving sibutramine 10 mg daily, compared to 1.21/o loss in patients taking placebo .[7] Sibutramine-treated patients also demonstrated improvements in HDL, LDL, and triglycerides in association with weight loss. In studies one year in duration or longer, the most rapid degree of weight loss was seen within the first 6 months. Up to 15% of subjects in short term investigations did not respond to treatment with sibutramine irrespective of dose. As could be expected after discontinuation of any weight loss regimen, study patients did have evidence of weight regain after stopping sibutramine.

The most commonly noted side effects of sibutramine include dry mouth, headache, insomnia, constipation, and anorexia. However, there has also been some concern regarding hypertension and tachycardia related to sibutramine use. In pooled data from over 2000 patients, fewer than 2.6% had a cardiovascular related event (rise in blood pressure, arrhythmia, or palpitations), and there has been no evidence of valvular lesions related to sibutramine treatment. These effects are consistent with sibutramine's mode of action, and are thought comparable to the effects of other serotonin-norepinephrine reuptake inhibitors.

Sibutramine is administered orally and has a half-life of 14-19 hours. The standard initial dose is 10 Ing daily in conjunction with a reduced calorie diet. This dose may be reduced to 5 mg for patients who can not tolerate the initial strength, or can be raised to 15 ing for patients who show no response after 4 weeks.

Use of sibutraine is contraindicated in persons with a history of recent MAOI inhibitor and centrally acting appetite suppressant use, as well as coronary artery disease, congestive heart failure, arrhythmias, hepatic failure, renal failure and uncontrolled hypertension. It has been shown to interfere with drugs such as cytochrome P450 inhibitors (i.e, cimetidine, ketoconazole, erythromycin), and decongestants (phenylephrine, ephedrine, pseudoephedrine). Sibutramine has not been shown to alter the efficacy of oral contraceptives nor atenolol.[6]

b. Orlistat (Xenical, NDA No. 20-766)

Otherwise known as tetrahydrolipistatin, orlistat is a product of Hoffman-LaRoche Pharmaceuticals which is presently in phase IV trials for the management of obesity. Through its action as an inhibitor of gastrointestinal and pancreatic lipases, it has been shown to have a dose dependent effect on dietary fat absorption. At a dose of 120 mg three times a day, orlistat has been noted to prevent absorption of up to 30% of fat intake. [8] A recent comparison between orlistat 120 mg TID and placebo demonstrated a mean weight reduction of 8.76 kg (-+0.37 SEM) and 5.81 kg (-+0.67 SEM) respectively.

($p<0.001$).[9] Other research has shown a 5% weight loss and significant improvements in lipid profiles and insulin requirements among orlistat subjects, compared to only 3.5% weight loss in placebo recipients.[10]

Orlistat is administered orally and has a half-life of 19 hours. It is not significantly absorbed into the bloodstream. A dose of 120 mg three times daily with meals is in accordance with current dosing recommendations.

Noted side effects of orlistat use include abdominal discomfort, oily stools, increased defecation, loose stools, and fecal incontinence. In meta-analysis of several studies comparing orlistat and placebo, most side effects occurred within the first week of treatment and were mild in nature. Long term studies of orlistat, reveal an incidence of gastrointestinal events ranging between 8-27%.

Because of the affect on fat uptake from the diet, there has been concern for orlistat's influence on the blood levels of fat-soluble vitamins. Meta-analysis has shown that levels of Vitamin A, D, and E were significantly reduced in orlistat treated individuals, but that most of these levels remained within a normal clinical range and could be supplemented. There had also been concern regarding a possible relation between orlistat nd breast cancer during phase III testing, Eleven cases of breast cancer were diagnosed in orlistat treated women compared to three placebo recipients. However, under further analysis, only 3 cases in the orlistat group, and 2 placebo cases were thought to have developed after starting treatment. Therefore, the incidence of breast cancer was deemed similar between the groups, In addition, animal studies have failed to show evidence of a link between orlistat and any neoplasms, including breast cancer.

Orlistat has not been shown to significantly affect the actions of multiple classes of antihypertensives, Dilantin, Glyburide, Digoxin, Cournadin, or oral contraceptives.[11]

E. Medical Devices

No medical devices are to be studied.

F. Study Questionnaires

Topics to be discussed may include frequency and length of exercise, type of exercise, and summaries of dietary intake.

G. Study Subjects

a. Inclusion Criteria

- Men and women between the ages of 18-65, with a BMI (30 are eligible to participate in the study.

b. Exclusion Criteria

- Poorly controlled hypertension, coronary heart disease, CEF, cardiac arrhythmias
- Hepatic or renal failure
- Stroke or epilepsy
- Pancreatitis or lipase deficiency
- Recent use of monoamine- oxidase inhibitors or appetite suppressants
- Insulin requiring diabetics or significant complications of diabetes
- History of weight reduction surgery
- Drug or alcohol abuse
- History of eating disorders such as anorexia, bulemia, or laxative abuse
- Women of child-bearing age not on reliable methods of contraception
- Use of any medications that can alter body weight, lipid or fat soluble vitamin levels
- Any clinically relevant condition

H. Recruitment of Subjects

Potential subjects will be recruited from within the medical center and the community via flyer and local advertisement.

I. Confidentiality of Study Data

All study subjects will be assigned a code number upon entry into the study. Only this number will be used in data collection. Data will only be accessible to study coordinators and will be stored in a secure location.

J. Potential Conflict of Interest

The investigators and the University do not have any proprietary interest in sibutramine or orlistat, and do not stand to benefit financially from the results of the investigation.

K. Location of the Study

All patient encounters and data collection will occur within clinical care areas of the New York Presbyterian Hospital.

L. Potential Risks

Risks for study participants include the potential side effects detailed in the study drug segment of this protocol. Patients may also experience discomfort with venipuncture and blood sampling. It is possible that study subjects may not respond to the study drugs, or that they may be disappointed with their degree of weight loss.

M. Potential Benefits

Obese patients stand to gain physical benefits from weight reduction through the pharmacological and behavioral interventions proposed. Society as a whole, may benefit from the establishment of a new method of short-term weight loss.

N. Alternative Therapies

Presently acknowledged methods of weight reduction, such as calorie restriction, energy expenditure through physical activity, and pharmacological treatments have all been incorporated into the study design. Severe calorie restriction could be disadvantageous if it prevented intake of essential nutrients. Excessive, strenuous, physical conditioning could possibly lead to physical injury.

O. Compensation to Subjects

Study subjects will receive $$ in the form of a check at the end of 26 weeks of participation. Payment will not be pro-rated if the subject does not complete the study.

P. Cost to Subjects

Subjects will not incur additional costs through participation in the study.

Q. Mnors as Subjects

The study will not involve the participation of minors.

R. Radiation or Radioactive Substances

Neither radiation nor radioactive substances are to be used during the course of this study.

S. References

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