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Effect of Rimonabant, a Cannabinoid-1 Receptor Antagonist, on Weight Loss in Hypothalamic Obesity

A. Study Purpose and Rationale:

Hypothalamic obesity is a rare cause of intractable weight gain seen in patients with structural damage to the hypothalamic region. This damage most commonly occurs as the result of a sellar tumor, surgical damage during removal of such a tumor or radiation to the area after tumor removal. Patients with structural hypothalamic damage may develop a syndrome of intense hyperphagia, hyperinsulinemia and insulin resistance leading to obesity. Craniopharyngioma and its treatment is the single most common structural cause of acquired hypothalamic damage (1). Hypothalamic obesity has been shown to occur in up to 50% of survivors of craniopharyngioma, a benign embryogenic sellar tumor, most often seen in children and adolescents. The overall incidence of craniopharyngioma in the general population is 1.5/million/year, making hypothalamic obesity extremely rare, however, for individuals with this syndrome the long term health and psychological effects of this syndrome can be devastating(1).

The pathogenesis of hypothalamic obesity is not well defined. In animal models, lesions to the ventromedial nucleus of the hypothalamus have been shown to induce a syndrome of hyperphagia, hyperinsulinemia, insulin resistance and obesity, similar to the syndrome seen in humans (1).

In humans, the degree of weight gain varies between individuals with structural hypothalamic damage. In a study by DeVile et. al., 63 survivors of childhood craniopharyngioma underwent MRI brain imaging in order to visualize the extent of hypothalamic damage seen after surgical tumor resection. The degree of damage visualized by MRI correlated to the amount of post-surgical weight gain.

Due to the close proximity of the pituitary stalk to the sellar tumors these patients often experience concomitant deficiencies of pituitary hormones including GH (growth hormone) and ACTH. Replacement of these hormones back to physiologic levels has not been shown to impact the incidence of obesity (1).

There are several mechanisms thought to contribute to hypothalamic obesity, including hyperphagia, autonomic dysregulation and impaired energy expenditure. The extreme hyperphagia that has been observed in patients after surgical resection of craniopharyngioma in particular has been extremely difficult to control clinically.

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Currently, there are very few treatment options for people with hypothalamic obesity. In one recent study Octreotide, a long acting somatostatin agonist, which works to attenuate insulin secretion of pancreatic beta cells, was shown to have a modest beneficial effect on weight loss in a small cohort of children with hypothalamic obesity. Unfortunately, this medication also has a number of adverse side effects (3).

To date, there are very few studies looking at the effect of weight loss drugs in this specific population.

Rimonabant, a selective cannabinoid-1 receptor antagonist, has been shown in randomized clinical trials to decrease appetite and induce weight loss in obese patients. Cannabinoid-1 receptors are located in a number of areas within the central nervous system including the hippocampus, cerebral cortex, cerebellum, limbic system and hypothalamus. These receptors are also found in a number of peripheral tissues including the liver and adipose tissue (4). The CB-1 receptor agonist, THC, has been shown to induce appetite stimulation and is often used in wasting syndromes such as AIDS and in patients with advanced cancer. The selective CB-1 receptor antagonist, Rimonabant, has been shown in several studies to reduce appetite, likely thorough central neuronal pathways involved in modulation of food seeking behavior. Rimonabant also exerts effects in the peripheral receptors such as adipose tissue and the liver. In recent studies, rimonabant has been shown to induce adiponectin release from adipocytes in vitro (4). Adiponectin is a key regulatory hormone release from adipocytes and has been shown to be associated with increased insulin sensitivity, decreased hepatic glucose production and suppression of lipogenesis. The CB-1 receptor antagonist, SR141716, was also shown to reduce fatty acid synthesis in the liver in mice (5). In a recent clinical trial, obese patients who took 20mg of rimonabant saw an overall 6kg weight loss after 1 year as compared to the placebo. These patients also saw an improvement in HDL and Triglyceride levels as compared to the placebo control.

I propose that Rimonabant administration in patients with hypothalamic obesity due to craniopharyngioma and treatment by surgical resection and radiation will have a positive effect on overall weight loss.

B. Study Design:
A randomized, placebo-controlled, double blind, crossover study looking at the effect of Rimonabant, a selective cannabinoid-1 receptor antagonist, in patients with hypothalamic obesity.
A cohort of 22 patients who have developed intractable hypothalamic obesity as a result of a craniopharyngioma and surgical resection (+/-) radiation therapy will be recruited. Each patient will undergo an initial 2 week screening period where they will receive diet and exercise education with a goal 600kcal daily deficit. After this initial screening, they will then be randomized, by computer generated randomization at a ratio of 1:1, to either (a) diet and exercise plus placebo or (b) diet and exercise plus 20mg of Rimonabant. The patients will be followed for a total of 6 months in each arm. At the end of the initial 6 months, each patient's weight (as an average of 3 weights) will be taken and percentage of body fat will be calculated. Blood samples will also be taken at this time for analysis of HDL and triglyceride levels.
The groups will then be crossed over to the opposite study arm for another 6 months. At the end of 1 year each patient's weight will again be measured and percentage of body fat will be calculated. The second set of blood samples will be taken for analysis of lipid profile. The data will be analyzed as the change in weight, percentage of fat and lipid levels from end of 6 months on placebo to end of 6 months on Rimonabant.

Power analysis:
This sample size of 22 patients was calculated based on a standard deviation in weight change of 10kg and an effect size of 6kg using a paired t-test. The standard deviation in weight change was obtained from a recent study looking at the effect of rimonabant in obese patients. The standard deviation in change of weight for patients taking 20mg of rimonabant for one year was found to be approx. 10kg. Our effect size of 6kg was also taken from the same study where they found an average weight loss of 6kg for patients taking rimonabant as compared to placebo.

C. Study Procedure:
Weight and percentages of total body fat will be measured in kilograms using a standardized body composition analyzer. Patients will come in for measurements and blood draws at the beginning of the study, at the end of the first six months and at one year when the final measurements will be taken. Each weight will be an average of 3 separate weights taken on the same day at time 0, 6 months and 12 months. Complete physical exams will be done at the beginning of the study and again at the completion of the study.
Study procedures do not differ in type or frequency from standard care that each participant would receive in the course of general physician care, with the exception of multiple blood draws at the end of 6 months and 1 year.
Each participant will remain in the study for the total duration of 1 year.

D. Study Drugs:
Rimonabant has not been approved by the FDA and is thus classified as an investigational drug; however, it has been approved in Europe where it is currently in use. Safety and efficacy has been tested in previous clinical trials where the most common side effects in patients taking a 20mg dose were found to be psychiatric disorder (6%) (including: depressed mood (5%) and anxiety (6%)), nausea (11%) and arthralgias (8%). The drug was not approved by the FDA due to the high rate of adverse psychiatric events occurring in people who were taking the drug as compared to the placebo group. There were 2 reported suicides that are attributed to taking the drug and one cardiac arrest in a patient with long QT syndrome.
Rimonabant will be administered orally in a 20mg daily dose.

D. Medical Devices: none

F. Study Questionnaire: none

G. Study Subjects:

Inclusion criteria: Patients will be included in this study if they meet the criteria for hypothalamic obesity occurring as the result of a craniopharyngeoma, surgery or

radiation with resultant damage to the hypothalamus. Patients must have survived the cranial insult in stable medical condition for at least 2 years after therapy. Each participant should have demonstrated an annual weight gain equal or greater to 2 standard deviations above the average annual weight gain for their age in the general population. Only people over the age of 18 will be considered for this study.

Exclusion criteria: Any patient with a history of a psychiatric disorder or long QT syndrome due to the current side effect panel of Rimonabant.

H. Recruitment of Subjects
Participants will be recruited mainly from the Obesity clinic at Colombia Presbyterian Hospital and the affiliated Endocrinology specialists in the area. They will be given information about the study in their physician's office and asked if they would like to speak to one of the investigators about participation.

I. Confidentiality of Study Data:
All information about participants will be kept in a secure on-site facility at CUMC. All study data will be coded using a unique coding system. No person information will be released to parties who are not directly involved in the research study.

J. Conflict of Interest: none

K. Location of the study:
The study will take place on site at Columbia Presbyterian University Hospital in a designated clinical care area.

L. Potential Risk:
There is a small risk of adverse psychiatric events including depression and anxiety which were the side effects of the study drug seen in previous clinical studies. Other more common side effects include gastrointestinal upset, fatigue and insomnia.
Each participant will undergo a psychiatric evaluation prior to beginning the study and will be monitored periodically for any adverse psychiatric side effects. Even with these safe guards in place, there is a small chance of death due to the drug that will be disclosed to the participant prior to enrollment in the study.

N. Alternative Therapies:
Participants will be informed of alternative weight loss therapies which include diet and exercise, appetite suppressants and commercial weight loss drugs available in the US.

O. Compensation: none

P. Costs to Subjects: none

Q. No minors will be enrolled in this study

R. No radioactive substances will be used in this study

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