Institutionen för klinisk vetenskap, intervention och teknik, Enheten för pediatrik

Severe Childhood Obesity: Behavioural and Pharmacological Treatment

AKADEMISK AVHANDLING
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ABSTRACT

Background
Childhood obesity is a chronic disease associated with increased morbidity, psychosocial problems and reduced life expectancy, all of which is today very common. Despite this, long-term studies of behavioural treatment of childhood obesity are currently lacking. In addition, behavioural treatment has often only a modest effect and the number of children and adolescents who drop out during treatment is very high. Therefore, additional treatment with antiobesity drugs may be of importance.
This thesis evaluates pharmacological and long-term behavioural treatment of severely obese patients in a hospital setting. It includes the first studies published evaluating the effect of three years of behavioural treatment, as well as one study in which the effect of the lipid intestinal uptake inhibitor orlistat is studied in prepubertal children. Finally, the effect of sibutramine, a drug that increases satiety, is studied in severely obese children with hypothalamic obesity and children with obesity in combination with aggravating syndromes.

Aims
The primary aims for the *behavioural treatment studies* were to investigate whether age when treatment is initiated had an effect on treatment outcome and whether the degree of obesity predicts treatment efficacy.
The secondary aims were to study whether gender, socio-economic factors, parental weight or age at obesity onset had any effect on outcome and, furthermore, to evaluate factors associated with risk for drop-out. In the *pharmacological studies* the aim was to study orlistat treatment of prepubertal children with regard to tolerance, safety and psychological well-being. The aim of the Sibutramine Study was to investigate whether the drug is effective for obese children who have other diseases that make behavioural treatment ineffective.

Material and Methods
All children were treated from 1998 to 2007 at the National Childhood Obesity Centre, Karolinska University Hospital, Huddinge. Papers I and II include, in total, 643 patients, 6–16 years of age, with simple obesity treated with behavioural treatment therapy for three years. The children were divided into three age groups based on their age at the start of treatment, 6–9, 10–13 and 14–16. In Paper II the subjects were further assigned to two groups: moderate obesity, < 3.5 BMI SDS, or severe obesity, > 3.5 BMI SDS.
In the Orlistat Study, Paper III, 11 severely obese prepubertal children (age 8.3–12.3 yrs), BMI SDS 5.3–9.2) were recruited for a 12-week open treatment. The children received the standard adult dose, i.e. 120 mg three to four times daily. Before, during and at the end of the study period the participants were investigated with psychological evaluation, blood chemistry and parameters reflecting obesity and fat mass.
The Sibutramine Study was a double-blind, placebo-controlled, cross -over study. 50 children (7–20 years of age) with hypothalamic obesity or obesity with aggravating syndromes were randomised in diagnostic pairs. The initial sibutramine/placebo dose was 10 mg. The treatment period was 20 + 20 weeks, followed by a 6-month open phase. The primary efficacy variable was change in BMI SDS.

Results
In the behavioural treatment studies, the decline in mean BMI SDS was most pronounced in the youngest age group ($P = 0.001$). Pronounced treatment effects were found in moderately and severely obese children in the younger age groups. No effect was observed in severely obese adolescents. Only a weak correlation was found between treatment effect during the first year and BMI SDS change from the start to the end of year three, $r = 0.51$ ($P < 0.001$). Only 30% in the oldest age group remained in treatment for three years.
The participants were able to comply with the treatment with orlistat and expressed a desire to continue the treatment after the study period. The side effects were mild and tolerable. No negative effects on psychological or physical well-being were detected.
In the Sibutramine Study there was a clinically and statistically significant difference ($P < 0.001$) between the active drug and placebo. The response of children with hypothalamic obesity ($P = 0.005$) was significant but less pronounced than that of children with non-hypothalamic obesity ($P = 0.001$). A continued reduction was observed during the open phase. The treatment was well tolerated by all children.

Conclusions
Behavioural treatment is successful when initiated at 6–9 years of life in both moderately and severely obese children. Age was the only dependent factor for treatment success and predictor for drop-out. Adolescents with severe obesity need special attention. Obese prepubertal children who used orlistat were able to reduce their fat intake and it is possible that orlistat could be used in motivated prepubertal children. Sibutramine might be a suitable aid for children with hypothalamic obesity and aggravating syndromes if sibutramine was approved by EMEA for this age group.

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