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ORIGINAL PAPER

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Addition of orlistat to conventional treatment in adolescents with severe obesity

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Abstract To investigate the efficacy and tolerability of orlistat in obese adolescents, a prospective, open-label, randomised, controlled pilot trial was performed. A total of 22 adolescents with exogeneous obesity were started on orlistat (120 mg tid) and a daily multivitamin preparation in addition to conventional treatment which included nutritional and lifestyle modification programmes. The control group consisted of 20 obese adolescents who had similar duration of follow-up under conventional treatment alone. Of the 22 patients, 7 dropped out within the 1st month of the trial due to side-effects attributable to orlistat. The remaining 15 patients on orlistat were followed for 5–15 months (average duration of treatment 11.7 ± 3.7 months). The control group was similar in age, sex, and duration of follow-up (10.2 ± 3.7 months, range 6–17 months) to the orlistat group. Compared to initial body weight, patients in the orlistat group lost -6.27 ± 5.4 kg, whereas those in the control group gained 4.16 ± 6.45 kg ($P < 0.001$) during the study period. Patients in the orlistat group lost $-7.65\% \pm 6.5\%$ of their initial body weight, whereas, those of the control group gained $5.7\% \pm 8.3\%$ ($P < 0.001$). The body mass index decreased in the orlistat group by -4.09 ± 2.9 kg/m^2 while it increased by $+0.11 \pm 2.49$ kg/m^2 in the control group ($P < 0.001$). Mild gastrointestinal complaints (frequent stools) were experienced by all patients in the orlistat group. *Conclusion*: Orlistat could be a useful adjunct in the treatment of severe obesity in adolescents; however, gastrointestinal side-effects limit its usefulness in almost one in three adolescents.

Keywords Adolescents · Children · Obesity · Orlistat · Treatment

Abbreviation BMI: body mass index

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Introduction

The prevalence and severity of obesity is increasing in the paediatric population [13]. This has resulted in an increasing trend in outcomes related to obesity, such as type 2 diabetes mellitus, in some countries [4, 11]. In addition, obesity-related complications such as sleep apnoea, hypertension, orthopaedic problems etc., cause significant morbidity even in severely obese children. The current clinical approach to the management of obesity in paediatric patients is behavioural therapy directed at reducing caloric intake and increasing physical activity. The success rate is not satisfactory with the current mode of management since most children are not able to follow a hypocaloric diet [1]. While pharmacotherapy is not yet available for treatment of childhood obesity due to safety considerations, there is hope that agents approved for use in adults will prove useful in adolescents and children.

The gastrointestinal lipase inhibitor orlistat has been used safely with varying effectiveness in obese adults [3]; however, there are no medium-term or long-term studies investigating tolerability and effectiveness in children and adolescents. We performed a prospective, open-controlled pilot study to investigate the efficacy and tolerability of orlistat in obese adolescents.

Subjects and methods

The subjects were recruited among the patients who were referred to study centres for evaluation and management of obesity. After obtaining approval of the institutional ethics committee, the patients were selected according to following criteria: (1) severe exogenous obesity, described as weight for height index >140% in otherwise healthy subjects, not associated with endocrinopathy, genetic syndromes or medications, (2) adolescents (Tanner stage 2 or higher) aged between 10–16 years, and (3) informed consent for the study.

Randomisation was done by alternation of successive patients who met the inclusion criteria stated above to receive conventional treatment alone or orlistat in addition to conventional treatment. A total of 22 patients in the treatment group received orlistat (120 mg tid) and a daily oral multivitamin preparation. The control group consisted of 20 obese patients matched for age, sex, pubertal stage and the degree of obesity. Both orlistat and control group patients were subjected to a lifestyle modification programme including diet (20% reduction in daily calories calculated for age and sex) and increase in activity level throughout the study period (at least 30 min of moderate exercise per day). This programme was administered by a team comprising a paediatric endocrinologist, paediatrician and a dietitian at each centre. The subjects were seen by the dietitian monthly and in the outpatient clinic every 2 months. Lifestyle modification was reinforced at each visit. A complete physical examination, including height and weight measurements, was carried out. Compliance with diet and exercise programme was judged according to rating by the parents as poor, fair or good.

Outcome measures included weight and body mass index (BMI) at the beginning of the study and at the last visit in the clinic. A *t*-test was used to evaluate differences between the two groups in parameters examined. The Mann-Whitney rank sum test was used for the parameters that did not follow a Gaussian distribution.

Results

The results are shown in Table 1. In the orlistat group, seven patients terminated the study within the 1st month of therapy due to gastrointestinal complaints attributable to orlistat. The remaining 15 patients who continued on orlistat, were followed for 5–15 months (average duration of treatment 11.7 ± 3.7 months). Five patients in the control group dropped out due to noncompliance with bimonthly clinic examinations. The remaining 15 obese adolescents in the control group who had a similar duration of follow-up (range 6–17 months; mean ± SD 10.2 ± 3.7 months, not significant) were compared with the 15 patients of the orlistat group.

Both orlistat and control groups were similar with regard to age and sex distribution (12.9 ± 2.4 years versus 12.5 ± 2.2 years respectively; five males and ten females in each group). Reported compliance with the diet and exercise programme were similar in both orlistat and control groups and was fair to poor after the first 2 months in all subjects.

At the initiation of the study, body weight was 82.1 ± 20.9 kg in the orlistat group and 73.9 ± 15.3 kg in the control group (not significant). BMI (median) and weight for height (median) was higher in the orlistat group compared to the control group (32.5 versus 31.2 kg/m^2, $P = 0.018$, and 171% versus 153%, $P = 0.026$, respectively).

At the last clinic visit, BMI was 30.5 ± 6.0 kg/m^2 in the orlistat group and 31.1 ± 4.2 kg/m^2 in the control group. Compared to initial body weight, the orlistat group lost -6.27 ± 5.4 kg (range +5 to −12 kg), while the control group gained 4.16 ± 6.45 kg, (range + 16.7 to −8.5 kg) ($P < 0.001$) during the study period. Patients in the orlistat group lost $-7.65\% \pm 6.5\%$ of their initial body weight, whereas those in the control group gained $5.7\% \pm 8.3\%$, $P < 0.001$. Two patients in the orlistat group and nine patients in the control group gained weight during the study.

There was a significant difference in ΔBMI (initial BMI-final BMI) between the two groups. BMI decreased in the orlistat group by -4.09 ± 2.9 kg/m^2 whereas it increased by $+0.11 \pm 2.49$ kg/m^2 in the control group ($P < 0.001$) (Fig. 1).

Mild gastrointestinal complaints (frequent stools) were experienced in all orlistat-receiving patients. Seven of these patients dropped out due to intolerable side-effects including gastrointestinal complaints (soiling, frequent defaecation; $n = 5$), mild hair loss ($n = 1$) and reported muscle cramps not associated with hypocalcaemia ($n = 1$).

Table 1 Patient characteristics and parameters examined in orlistat and control group of obese adolescents (mean ± SD)

	Orlistat group	Control group	*P*
Age (years)	12.9 ± 2.4	12.5 ± 2.2	Not significant
Duration of treatment (months)	11.7 ± 3.7	10.2 ± 3.7	Not significant
[a]Initial weight for height (%)	171	153	0.026
[a]Initial BMI (kg/m^2)	32.5	31.2	0.018
BMI at the end of the study (kg/m^2)	30.5 ± 6.0	31.1 ± 4.2	Not significant
Δ BMI (kg/m^2)	-4.09 ± 2.9	0.11 ± 2.49	< 0.001
Weight change (kg)	-6.27 ± 5.4	4.16 ± 6.45	< 0.001
Percentage weight change	-7.65 ± 6.5	5.7 ± 8.3	< 0.001

[a]Median values are given for these parameters due to non-Gaussian distribution of the data

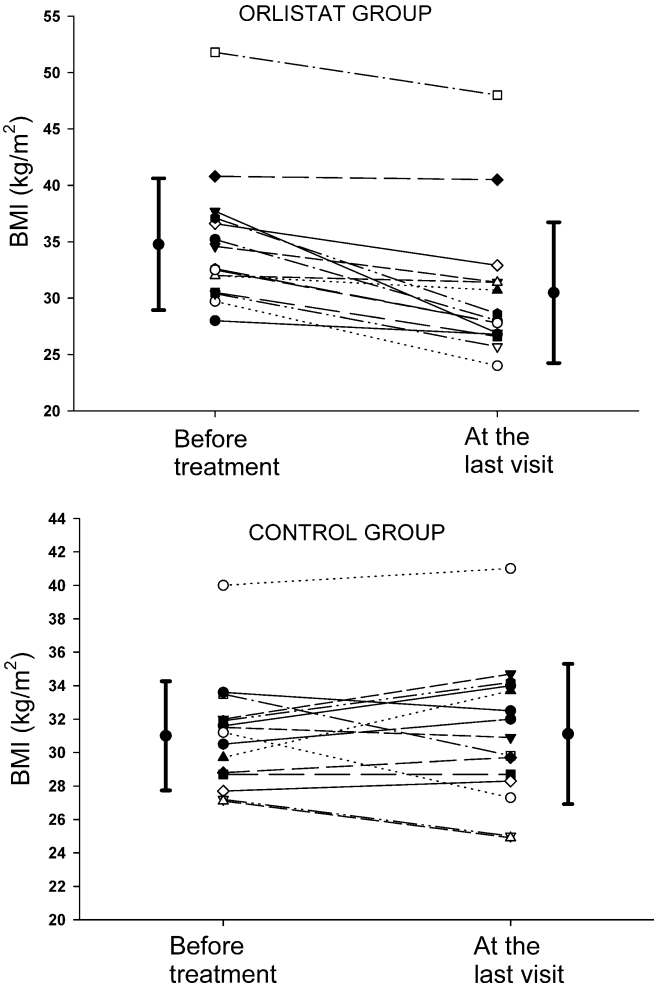

Fig. 1 Change in BMI during the study period in obese adolescents. Individual values and group mean ± SD are given. **a** Orlistat group. **b** Control group

Discussion

This investigation shows that orlistat treatment promoted weight loss and improvements in BMI which were sustained over the study period (up to 15 months of duration). In contrast, control adolescents continued to gain weight and their BMI showed either no change or slight increases, despite efforts of lifestyle intervention.

It is well known that low calorie diets are commonly prescribed, but rarely effective in achieving long-term weight loss in children [1]. Thus, therapy with a pharmacological agent which is safe and effective would be very beneficial in achieving weight loss in severely obese children. There are only two studies addressing the efficacy of orlistat in paediatric age group. In a short-term (3 month) uncontrolled study, 20 adolescents (age 14.6 ± 2.0 years; BMI 44.1 ± 12.6 kg/m^2) had a decrease in both weight (−4.4 ± 4.6 kg) and BMI (−1.9 ± 2.5 kg/m^2) [6]. In another uncontrolled study, a 4 kg weight loss was reported in 11 prepubertal children within 3 months [8]. A follow-up of former study was recently published demonstrating similar results at 6 months of treatment [7]. There are no medium-term studies published in paediatric population regarding efficacy and tolerability of orlistat.

In adults, medium-term trials (12–24 months) show that orlistat, combined with dietary intervention, has a minor supplementary effect on weight loss (−3.5 kg on average) [9]. In randomised, controlled trials of up to 2 years duration, orlistat plus a hypocaloric diet produced significantly greater weight loss than placebo ($P < 0.001$). In the maintenance phase, patients taking orlistat had less weight regain than did placebo recipients. The weight reduction with orlistat was also associated with a significant improvement in control of cardiovascular risk factors ($P < 0.05$) [12]; however, a meta-analysis of three of the four available comparative trials lasting 2 years failed to conclude that orlistat prevents the onset of type 2 diabetes. Likewise, there is no firm evidence that orlistat lowers cardiovascular morbidity or mortality [9].

In the current study, we report the results of 15 adolescents who remained on orlistat for an average duration of 11.7 months. We show that weight loss reported by short-term treatment with orlistat is maintained in the medium-term in adolescents. BMI decreased significantly in patients of the orlistat group compared to the control group. However, none of the patients was able to achieve a BMI that is normal for age.

Although orlistat was well tolerated in the majority of obese adolescents, in approximately 30% (7/22) of the patients, side-effects were severe enough to discontinue the treatment. These side-effects were all gastrointestinal, except in one patient with mild diffuse hair loss and another with muscle cramps. The hair loss was not severe and continued another 2 months after discontinuation of orlistat. Reported muscle cramps in another patient were not associated with hypocalcaemia and did not recur after discontinuation of treatment. Vitamin D levels were not measured. However, a recent study reported that orlistat treatment significantly reduced vitamin D levels in a month despite a daily multivitamin supplementing 400 U of vitamin D [5]. Thus, close monitoring of vitamin D concentrations in adolescents who take orlistat seems to be necessary.

In our experience and as seen in our control group, diet and lifestyle intervention alone, at best, only stops further increase in BMI, but does not decrease the degree of obesity in adolescents. Although we did not systematically analyse the compliance with lifestyle modification, parents' rating of compliance was generally poor to fair in all subjects in both groups. Our subjects were seen monthly by the dietitian and bimonthly in clinic during the study. A more vigorously and frequently monitored lifestyle intervention programme could have resulted in better outcome in both groups. However, noncompliance with the diet and exercise programme in the paediatric age group has been observed by other investigators [2]. A recent multicentre

study of nutrition intervention in 1300 children was deemed a failure when the drop-out rate exceeded 90% [10]. Indeed, this low success rate in lifestyle modification is the main motivation for studies investigating pharmacological agents in the treatment of obesity.

We conclude that orlistat could be a useful adjunct in the treatment of severe obesity and obesity-related comorbid situations to facilitate weight loss in adolescents. However, gastrointestinal side-effects limit its use in almost one in three adolescents. The true benefit of orlistat versus conventional therapy remains to be determined in a larger placebo-controlled study. Furthermore, long-term effects on weight and obesity-related risk-factors remain to be determined.

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