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The Effects of Orlistat Treatment Interruption on Weight and Associated Metabolic Parameters

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Abstract: Due to the insurance companies' restrictions, partial reimbursement of orlistat treatment in the Czech Republic is restricted to obese diabetics with BMI >35 who are concurrently treated pharmacologically for dyslipidaemia, hypertension or ischaemic heart disease, with compulsory interruption of minimum 3 months, only after which the treatment can be resumed for another year. We evaluated 32 patients with Type 2 diabetes who underwent such course of treatment, with view of establishing whether the interruption has any detrimental effect on the success of the therapy in terms of weight loss and diabetes compensation. The treatment was well tolerated, producing statistically significant decrease in BMI and triglyceride levels during the first year, which was maintained in the second year. Fasting glucose levels were improved at nearly-significant level. The interruption in treatment between the first and second year had no marked detrimental effect, although the relative failure of the second treatment year to bring further benefits to the patients can certainly be at least partially attributed to this treatment gap.

Introduction

Orlistat is a long-established, non-systemic acting gastrointestinal lipase inhibitor used for treatment of obesity. In the Czech Republic, its use is partially reimbursed by the health insurance companies, pending stringent criteria: obesity of BMI >35, presence of diabetes and concurrent pharmacological treatment for at least one other comorbidity: dyslipidaemia, hypertension or ischaemic heart disease. Furthermore, proved ability to lose 3 kg of weight under the guidance of prescribing physician before commencing the orlistat treatment has to be documented, as well as proven record of continuing weight loss after inception of orlistat of further 3 kg until the next visit at the prescribing physician. Moreover, when such criteria are met, orlistat can only be prescribed for 12 months only, after which an interruption of at least 3 months and the presence of all inclusion criteria is necessary to qualify for another year of treatment.

We tested retrospectively 32 patients with Type 2 diabetes who underwent such 27-month long treatment in order to establish to what extent is such enforced treatment gap beneficial, neutral in its effect or detrimental to the patients.

Materials and methods

32 patients, all women, (mean age 57.4 years, ±6.4SD, median 57 years) of the department's obesity clinic treated between 2004 and 2006 were retrospectively enrolled into this study.

Statistical description of measured parameters (BMI, GLY – glycaemia, HbA1c – glycosylated haemoglobin, CHOL – total cholesterol, LDL cholesterol and TGL – triglycerides) before the commencement of treatment, at the end of the first year, after he pause at the beginning of the second year of treatment and at the end of the second year, were calculated, and are listed in the Tables 1 and 2.

Methods

Body mass index was calculated from the patient's weight and height according to the formula: BMI = weight (in kg) / height (in m^2). Glucose, total cholesterol and triglyceride levels were obtained in automatic analyser Modular SWA, Roche, Switzerland; LDL cholesterol levels were calculated according to the Friedwald's formula, glycosylated haemoglobin was obtained by HP liquid chromatography. The normal range for glycosylated haemoglobin was calibrated according to the IFCC. The formula for transforming the DCCT calibration to the IFCC is as follows: IFCC = 1,093* DCCT-2,15, or, if only approximate numbers are required IFCC = DCCT-2 percentage points.

Statistical analysis

Statistical analysis was performed using S.A.S. (Statistical Analysis Software) release 8.02 and STATISTICA release 5.1.

Basic descriptive statistical data such as average, SD, distribution, median, quartile range, minimum and maximum were obtained for all measured parameters in the set as a whole and in each subgroup. Selected statistical data were also plotted into box & whisker diagrams. Non-parametric paired test (SIGN test) was used to compare distribution of individual parameters in various groups and subgroups. To test relationships between parameters, Spearman correlation coefficient was used due to the non-normal distribution of parameters.

Table 1 – Descriptive statistics. First year of treatment

	Beginning					End			
	N	mean	SD	median		N	mean	SD	median
BMI	32	41.4	5.80	41.5	BMI	32	38.2	5.01	37.5
GLY	27	9.2	3.40	8.4	GLY	26	7.7	2.77	7.3
HbA1c	17	5.9	2.12	5.2	HbA1c	19	6.2	2.13	5.5
CHOL	23	5.5	0.91	5.5	CHOL	24	5.0	0.75	4.9
LDL	21	3.2	0.63	3.4	LDL	21	3.0	0.57	3.1
TGL	23	2.2	0.94	2.1	TGL	23	1.8	0.64	1.7

Table 2 – Descriptive statistics. Second year of treatment

	Beginning					End			
	N	mean	SD	median		N	mean	SD	median
BMI	32	38.5	4.50	38.9	BMI	30	37.9	5.56	38.2
GLYK	25	8.6	4.01	7.4	GLYK	24	7.8	3.28	6.8
HbA1c	22	5.9	2.12	5.5	HbA1c	22	5.8	2.13	5.3
CHOL	23	4.9	0.93	4.9	CHOL	26	5.1	1.07	4.9
LDL	23	2.8	0.66	2.9	LDL	23	2.8	0.71	2.7
TGL	23	2.0	0.94	1.9	TGL	25	2.2	1.63	1.9

Results

1. We established the effect of orlistat in each of the years separately.

BMI During the first year, Spearman correlation coefficient showed statistically significant decrease in BMI at $p < 0.0001$, in the second cycle, no such significant decrease was found (Figure 1).

Glycaemia No significant changes in glucose levels were found, although in the first cycle, the glucose level decrease nearing statistical significance at $p = 0.09$ (Figure 2).

Total cholesterol No significant changes in levels of cholesterol were found.

LDL cholesterol No significant changes in levels of cholesterol were found.

Triglycerides During the first year, Spearman correlation coefficient showed statistically significant decrease in triglycerides at $p=0.002$, in the second cycle, no such significant decrease was found.

2. We looked at statistically significant differences between the end of the first year of treatment and then at the beginning of the second year of treatment, i.e., during the 3 months without therapy, did any of the tested parameters changed significantly?
   No such change was found in any of the parameters.
3. We looked at the development of each parameter during the first year of treatment and compared it to the development in the second year, testing whether one trend (increase, decrease or stationary) during the first year bears any relation to the trend (same or different) in the second year.

BMI, glycaemia, TGL and glycosylated haemoglobin No such relationship was found.

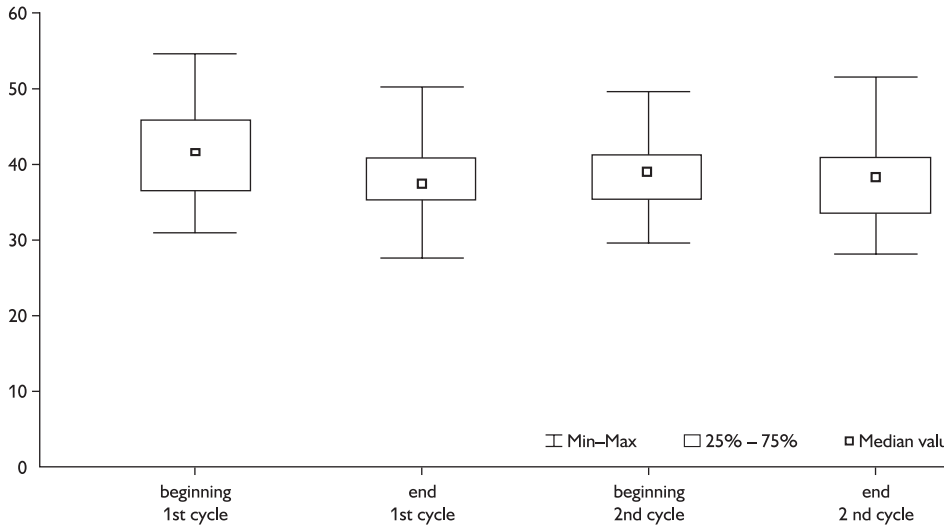

Figure 1 – Box and Whisker Plot BMI.

Total cholesterol Negative correlation was found, i.e. when total cholesterol during the first year was decreasing, in the second year it showed a tendency to increase, at p=0.001

LDL Similar negative correlation between the first and second year was found, nearing statistical significance at p=0.08

Discussion

Given the nature of orlistat prescription in the CR, our work is somewhat unique in being able to elucidate the consequences of interruption in orlistat treatment, viewed at the background of plenty of data on uninterrupted treatment of patients with Type 2 diabetes.

In a non-diabetic population, apart from landmark study XENDOS [1], data is limited for longer than 1-year treatment period. Our data support the findings by the XENDOS study group where the risk of developing type 2 diabetes was 37% lower in people treated with orlistat plus lifestyle intervention compared with lifestyle intervention alone, as reflected in the reduction of insulin resistance syndrome (IRS) hallmarks (insulin, glucose, glycosylated haemoglobin, total cholesterol, LDL and HDL cholesterol and triglyceride levels).

Weight loss during the four years of the XENDOS study was progressively smaller (–11.4 kg at one year vs. –6.9 kg at four years), again, a trend repeated in our smaller-scale study.

Reaven et al. [2] examined 1700 obese individuals treated for 1 year with orlistat. He stratified the whole group according to the triglyceride and HDL levels

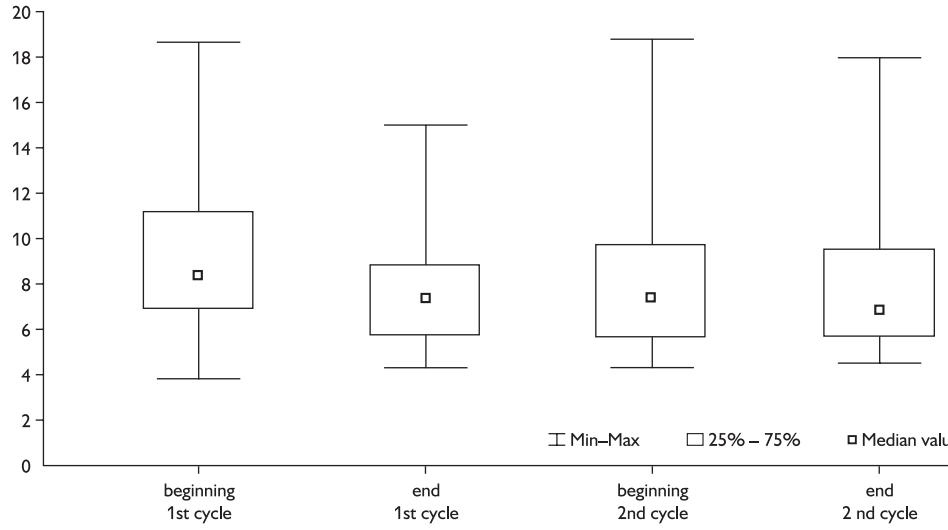

Figure 2 – Box and Whisker Plot Glykemie.

to those with insulin resistance syndrome (defined as the highest quintile for triglycerides level and lowest quintile for HDL cholesterol level) and without IRS (the lowest quintile for triglycerides and highest for HDL cholesterol), and compared the effect of orlistat on these groups. Weight loss in patients with IRS was associated with significant decreases in fasting insulin and triglyceride levels, and significant increase in HDL; findings which were not repeated in patients without IRS.

In studies measuring effect of orlistat in patients with established Type 2 diabetes treated with diet or medication, either oral antidiabetic agents or insulin, the results are repeated across the spectrum of available medications. Hollander [3] examined the effect of adding orlistat to established sulphonylurea treatment, to the effect of 4.6% weight loss in the orlistat group vs. 1.7% in the placebo group ($p<0.001$) after one year, with statistically significant decrease in glycosylated haemoglobin in the treatment group. Bray [4] reported results in Type 2 diabetics treated with exogenous insulin. The orlistat group achieved greater weight loss (–3.9% vs. 1.3%, $p<0.001$), and greater reduction in HbA1c and LDL cholesterol. Miles [5] reported results in patients with Type 2 diabetes treated with metformin. Again, orlistat group achieved greater weight loss (–4.6% vs. 1.7% in the placebo group, $p<0.001$), 61% of patients in the orlistat group reduced HbA1c by more than 0.5 percentage points and LDL decreased by 2.8% in the treatment group as opposed to the increase by 3.9% in the placebo group.

Conclusion

Treatment of diabetic patients with orlistat is well tolerated, and produces significant weight loss during the first year of treatment, which is maintained in the second year of treatment, despite the 3-month treatment gap between the first and second year.

The gap between the first treatment year and the second treatment year had very little detrimental effect on the weight loss, or on associated improvements in tested parameters of diabetes and insulin resistance that were achieved. However, the second year, probably also due to the interruption of treatment, did not produce further statistically significant improvement in BMI or other tested parameters.

During the first year of treatment, triglyceride levels decreased significantly, whilst glucose levels decreased with near-statistical significance. In the second year, these reductions in levels were maintained.

Statistically significant decrease of total cholesterol in the first year led to an increase in its levels during the second year. This trend was replicated, albeit only at near-significant level in LDL cholesterol levels.

The absence of more statistically significant changes in tested parameters in concordance with other published data is explained by the small scale of this study on a relatively heterogeneous population of Type 2 diabetics.

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