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Lipase inhibition by orlistat: effects on gall-bladder kinetics and cholecystokinin release in obesity

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SUMMARY

Background: Obese subjects are at risk of developing gallstones as a result of the obese state and during weight reduction.
Aim: To study whether orlistat, by lipase inhibition, impairs gall-bladder emptying, thus further predisposing weight-losing obese subjects to gallstone formation.
Methods: Patients entering a randomized clinical trial of 1 month of diet, followed by treatment with placebo, 3×60 mg orlistat or 3×120 mg orlistat, underwent gall-bladder emptying studies measured by ultrasound. Meal-induced cholecystokinin release and gall-bladder emptying were investigated at the start, at randomization and after 1 and 12 months.
Results: One month of dieting did not change gall-bladder emptying and cholecystokinin release. After 1 month, placebo treatment resulted in a decreased fasting volume of 11%, compared with increases of 26% and 47% with 60 and 120 mg orlistat, respectively. Gall-bladder emptying increased by 9% with placebo and decreased by 15% and 53% with 60 and 120 mg orlistat, respectively. Fasting cholecystokinin values and cholecystokinin release decreased significantly in the orlistat group. After 1 year, a persistent but attenuated effect of orlistat on gall-bladder emptying and cholecystokinin release remained. Three of 40 patients developed gallstones, two on placebo with major weight loss and one on 60 mg orlistat.
Conclusions: One month of lipase inhibition by orlistat significantly impaired gall-bladder motility, which persisted to some extent after 1 year. Obese subjects with diabetes or hyperlipidaemia, who are more at risk of gallstones, should be followed carefully.

INTRODUCTION

Obesity is a chronic and stigmatizing disease with serious health, economic and psychosocial consequences. It is an important risk factor for many medical complications involving the cardiovascular, respiratory, urogenital and musculoskeletal systems.[1–3] Obesity also has relevance for gastroenterologists as gastro-oesophageal reflux disease, gallstones and cholecystitis, pancreatitis and non-alcoholic fatty liver disease are more prevalent in obese subjects. Moreover, overweight and obesity are associated with an increased risk of oesophageal, gall-bladder, pancreatic and colon cancer.

Most of these disease risks improve with weight loss, but the case is different for gall-bladder disease. Firstly, obese patients are at risk of developing gallstones. This risk increases linearly with the body mass index, at least in women, and with the degree of central fat distribution in men.[4–9] Secondly, they are at increased risk during weight reduction. After 1–4 months' adherence to a very-low-calorie diet, gallstones occur in 11–26% of patients and biliary sludge in 6–21%.[10–13] After bari-

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atric surgery, up to 36% of patients develop gallstones and 49% show biliary sludge.[14–17] Previous studies have identified numerous factors associated with an increased risk, including a high body mass index, a high waist/hip ratio as a measure of central obesity, a large and fast body weight loss, a low fat content in formula diets, prolonged fasting periods and high initial serum triglycerides and insulin.[11, 12, 18–22]

Increased cholesterol synthesis and bile supersaturation, cholesterol nucleation-promoting factors and gall-bladder motility disturbances are factors involved in the pathogenesis of gallstone formation.[22–25] Related to the obese lifestyle of skipping breakfast and lunch, or as a result of frequent dieting, prolonged periods of fasting are present, resulting in a dismal combination of an enlarged gall-bladder and prolonged episodes of high lithogenicity of bile.[21, 22, 26–29] Whilst losing weight, the mobilization of peripheral fat deposits is superimposed on the already present metabolic defect.[30] Sub-optimal gall-bladder contraction in response to sub-optimal cholecystokinin release may also contribute. The rather complex action and feedback control of cholecystokinin have been clarified with the use of specific cholecystokinin receptor antagonists, such as loxiglumide.[31] Gall-bladder contraction appears to be a specific cholecystokinin-controlled motor event, not governed by other regulatory peptides or gastrointestinal hormones.[32, 33] Fat and proteins are, on a molar basis, equipotent in stimulating cholecystokinin secretion.[34] Also, the chain length and degree of saturation of fatty acids, micellar solubilization and emulsification determine the magnitude of cholecystokinin release.[35–38] Pancreatic enzyme activity and thus digested nutrients are a prerequisite for cholecystokinin release, as has been demonstrated by the intravenous infusion of fat and in severe pancreatic insufficiency and coeliac disease.[31, 39–42]

Orlistat (tetrahydrolipstatin), a chemically synthesized hydrogenated derivative of lipstatin (a natural product of *Streptomyces toxytricini*), is a potent and specific inhibitor of gastric and pancreatic lipase and carboxylester lipase through covalent binding to serine, the active site of the enzyme. In a dose-dependent manner, orlistat has been shown to inhibit the absorption of fat and to increase faecal fat excretion, and thus to induce a significant weight loss in combination with a low-calorie diet.[43–45]

We hypothesized that lipase inhibition might result in reduced cholecystokinin release and decreased gall-bladder motility, and thus might predispose obese patients treated with orlistat to gallstone formation. Therefore, we decided to investigate gall-bladder kinetics and cholecystokinin release in patients entering a double-blind, placebo-controlled study, before and 1 and 12 months after randomization to placebo, 3×60 mg orlistat and 3×120 mg orlistat. As the institution of an energy- and fat-restricted diet, necessary to induce weight loss and to mitigate complaints of orlistat-related steatorrhoea, might interfere with gall-bladder emptying and cholecystokinin release, the effect of 1 month dietary therapy alone was also investigated.

PATIENTS AND METHODS

Patients

Adults with a body mass index between 28 and 43 kg/m^2 were invited to enter a weight loss programme and simultaneously to participate in an optional study examining gall-bladder kinetics. The weight loss programme consisted of an energy- and fat-restricted diet, exercise and behavioural modification. After 1 month of diet, adults were randomized to receive placebo, 3×60 mg orlistat or 3×120 mg orlistat. The gall-bladder kinetics were studied at the start (T_0), at randomization (T_1) and after 1 month (T_2) and 1 year (T_3) of drug treatment.

The exclusion criteria consisted of the usual contraindications for intended weight loss. More specific orlistat-related contraindications consisted of significant gastrointestinal disorders, such as inflammatory bowel disease or gastrointestinal bleeding, symptomatic cholelithiasis, nephrolithiasis, pancreatic disease and the use of medications which could be influenced by fat malabsorption, such as anticoagulant therapy and contraceptive drugs. With regard to the present gall-bladder study, patients with a history of gall-bladder disease, cholecystectomy, diabetes mellitus, bariatric surgery, gastrectomy or vagotomy were excluded. Also, medication that interfered with gastrointestinal function, such as prokinetic drugs, colestyramine, non-steroidal anti-inflammatory drugs (NSAIDs), etc., were prohibited. The study protocol was approved by the Medical Ethical Committee of our hospital and written informed consent was obtained from each individual before study entry.

Apart from the medical history and physical examination, each patient's obesity history was taken. Body

weight and height and waist and hip circumferences were measured and these measurements were repeated at each monthly visit. Fasting blood samples were taken for electrolytes, kidney and liver function tests, lipid profile, glucose and insulin at the start, at randomization and 1 month and 1 year later. Ultrasonography of the gall-bladder and kidneys to investigate the presence or formation of gallstones and renal stones was also taken at these times.

A dietary history was taken by the dietician and patients were asked to submit a 4-day diary, including two week days and two weekend days. This 4-day diary was also submitted at randomization and after 1 month and 1 year of follow-up. The World Health Organization formula was used to calculate the basal metabolic rate, which was multiplied by 1.3 to obtain the estimated daily energy expenditure.[46] The prescribed diet corresponded to the estimated total energy expenditure minus 2500 kJ (600 kcal), with a minimum intake of 5000 kJ (1200 kcal). The fat content was adjusted to 30% of the total energy intake, equally divided over saturated, mono-unsaturated and poly-unsaturated fat. After 6 months, the diet had to be adjusted to produce further weight loss. As body weight was lost, the caloric requirements decreased proportionally and, therefore, for each kilogram of weight loss, a reduction of 125 kJ/day (30 kcal/day) was required with a maximal reduction of 1250 kJ (300 kcal). Those with an already minimal intake of 5000 kJ (1200 kcal) were allowed to reduce their intake to 4200 kJ (1000 kcal).

Methods

Gall-bladder volumes were calculated from the real-time ultrasonographic dimensions of the gall-bladder using the ellipsoid model: gall-bladder volume equals $0.52(L \times W \times H)$, where L is the maximum longitudinal dimension, W is the width and H is the height of the gall-bladder. The ellipsoid model correlates well with the more tedious sum-of-cylinders method.[47–49] Ultrasonography was always performed by the same observer using an Aloka SSD-650CL (Aloka Co. Ltd, Tokyo, Japan).

Patients were investigated in the supine position after an overnight fast at the start (T_0) and at the same time after 1 month of an energy- and fat-restricted diet (T_1). One month (T_2) and 1 year (T_3) after randomization to either placebo or orlistat, these investigations were repeated. The gall-bladder volume was assessed twice in the fasting state. The mean of these values was taken as the fasting basal gall-bladder volume. Thereafter, the study medication was taken, followed by a standard test meal consisting of a pancake containing 2827 kJ (673 kcal), with 31.3 g fat (42% of total energy), 25.7 g protein and 78.4 g carbohydrates, and 150 mL of a glucose 10% solution; 10, 20, 30, 45, 60, 75 and 90 min after the test meal, the gall-bladder volumes were measured again. The residual volume was defined as the gall-bladder volume at 90 min after the test meal; the ejection volume was obtained by subtracting the residual volume from the fasting volume. The percentage of gall-bladder emptying after 90 min was calculated as the fasting volume minus the residual volume, divided by the fasting gall-bladder volume, multiplied by 100. The area under the post-prandial gall-bladder volume vs. time curve was calculated using the trapezoidal rule (*AUC*; mL.90 min).

Blood samples for cholecystokinin levels were taken twice in the fasting basal state and at 15-min intervals up to 1 h after the consumption of the test meal. To prevent an olfactory response to the test meal, which could lead to premature gall-bladder emptying (cephalic phase) or to an early cholecystokinin release, the meals were prepared and stored elsewhere. The mean fasting cholecystokinin was taken from the two fasting levels. The highest cholecystokinin level (peak cholecystokinin) and the timing of occurrence were also analysed. The incremental cholecystokinin value was calculated as the difference between the highest value and the value at the start. In addition, integrated plasma cholecystokinin concentrations were calculated as the area under the plasma cholecystokinin concentration–time curve (*AUC*; pM.60 min). Plasma concentrations of cholecystokinin were measured by a sensitive and specific radioimmunoassay using antibody T204.[50] This antibody binds to all carboxy-terminal cholecystokinin peptides containing the sulphated tyrosyl region without binding to gastrin. The detection limit of the assay was 0.5 pmol/L plasma. Blood samples were stored in ice and maintained at − 20 °C until measurement. All samples were measured in one run.

Statistical analysis

As this investigation was intended to be an observational study and part of a double-blind randomized trial, no power analysis was performed. Descriptive data are presented as the mean with the standard

deviation (s.d.) and changes are given as the mean of the difference with the standard error of the mean (S.E.M.). For comparison between groups, analysis of variance (ANOVA), with Bonferroni's correction for multiple comparisons, was used. The Kruskal–Wallis test was used for data that were not normally distributed. When groups were dissimilar at the start, the initial value was entered as a covariate, or proportional changes were studied. For paired data comparisons, the paired test or the Wilcoxon signed rank test was used. Relationships between gall-bladder characteristics and body weight or weight loss were tested by Pearson's r or Spearman's ρ correlation statistics. The influence of the achievement of a successful weight loss of 10% at 1 year was studied by univariate analysis with gall-bladder and cholecystokinin characteristics as dependent variables and the treatment group as a covariate; in addition, the interaction between weight loss and treatment was taken into account. To investigate changes in time, univariate analysis of repeated measurements was used. When three comparisons were made, the P value was set at 0.016. Otherwise, a two-tailed P value of < 0.05 was considered to be significant.

RESULTS

Sixty patients entered the weight loss programme; eight patients had undergone a cholecystectomy in the past, five females appeared to have multiple asymptomatic stones in the gall-bladder and two were excluded because of late study entry. Two female patients had one asymptomatic large gallstone in the gall-bladder and one male and two females refused participation. Therefore, 40 patients (eight males and 32 females), with an age (mean ± s.d.) of 45.5 ± 9.3 years, a body weight of 108.9 ± 14.2 kg and a body mass index of 37.4 ± 3.9 kg/m^2, were analysed at the start (T_0) and after 1 month of energy and fat restriction (T_1). Twelve patients were randomized to placebo treatment (two males and 10 females) and 14 patients to either 60 mg (four males and 10 females) or 120 mg (two males and 12 females) orlistat, and were studied again 1 month later (T_2). After 1 year (T_3), data were available for 32 patients (six males and 26 females). Eight patients withdrew or failed to participate in the gall-bladder study after 1 year (three subjects on placebo, two subjects on 60 mg orlistat and three subjects on 120 mg orlistat). Nine patients belonged to the placebo group (one male and eight females), 12 to the 60 mg orlistat group (three males and nine females) and 11 to the 120 mg orlistat group (two males and nine females).

Gall-bladder kinetics 1 month after energy and fat restriction (Table 1)

The dietary prescription using the World Health Organization formula resulted in a mean 1820 kJ (435 kcal) deficit when compared with the dietary history of the

Table 1. Paired comparison between values at the start (T_0) and after 1 month of energy and fat restriction (T_1) in 40 subjects. Values are given as the mean ± standard deviation

	T_0	T_1
Body weight (kg)	108.9 ± 14.2	106.7 ± 14.1*
Body mass index (kg/m^2)	37.4 ± 3.9	36.6 ± 3.9*
Energy intake (MJ)	8.3 ± 2.8	5.8 ± 1.4*
Fat intake (g)	95.0 ± 39.1	50.8 ± 17.2*
Fat intake as percentage of total energy intake	39.1 ± 5.5	32.9 ± 6.8*
Fasting gall-bladder volume (mL)	30.1 ± 12.7	27.4 ± 11.9
Residual volume (mL after 90 min)	12.2 ± 9.8	10.1 ± 7.5
Ejection volume (mL)	18.0 ± 8.7	16.8 ± 8.6
Percentage of gall-bladder emptying	62.0 ± 18.2	62.8 ± 20.7
AUC gall-bladder (mL.90 min)	2022 ± 1035	1878 ± 974
Fasting CCK value (pM)	1.68 ± 0.77	1.49 ± 0.75
Peak CCK value (pM)	2.99 ± 1.04	2.99 ± 1.18
Time of peak value (min)	42.0 ± 14.5	43.1 ± 13.7
Incremental CCK (pM)	1.24 ± 0.65	1.50 ± 0.80
AUC CCK (pM.60 min)	162.5 ± 64.4	158.9 ± 60.9

AUC, area under the curve; CCK, cholecystokinin.
* $P < 0.001$.

dietician and a 590 kJ (140 kcal) deficit when compared with the 4-day diary. The diary after 1 month demonstrated a significant calorie deficit of 2428 kJ (578 kcal) and a decrease in fat intake, both in grams (44 g less) and percentage of the total energy intake (6.7% less). This resulted in a mean 1-month weight loss of 2.3 kg (1.2% of initial weight or 0.8 kg/m^2 units of body mass index). The fasting and residual gall-bladder values and gall-bladder emptying values were unchanged. The cholecystokinin values were similar.

Gall-bladder kinetics and lipase inhibition

Effect of 1-month treatment with lipase inhibitors (Table 2) — intra-group comparison. Placebo-treated patients lost a mean (± S.E.M.) of 1.1 ± 0.5 kg. The fasting and residual volumes, percentage of gall-bladder emptying, ejection volume and *AUC* of the gall-bladder decreased, but none of the changes were significant.

Patients treated with 60 mg orlistat lost 1.7 ± 0.4 kg. They showed a significant increase in the fasting gall-bladder volume, whereas the residual volume, ejection volume and *AUC* increased to some extent, but not significantly.

Patients treated with 120 mg orlistat showed a decrease of 2.5 ± 0.4 kg in body weight. All kinetic parameters increased and the percentage of gall-bladder emptying decreased, with significant increases in the fasting gall-bladder volume and *AUC* of gall-bladder emptying.

Taking the orlistat-treated groups together, the increases in fasting gall-bladder volume (mean ± S.E.M., 7.7 ± 1.8 mL), residual volume (4.0 ± 1.6 mL), ejection volume (3.8 ± 1.6 mL) and *AUC* of gall-bladder emptying (418.7 ± 149.6 mL.90 min) were significant. They lost 2.1 ± 0.3 kg of body weight.

The fasting, peak and incremental cholecystokinin values and the *AUC* of cholecystokinin release decreased in all three groups. In the 120 mg orlistat group, the fasting cholecystokinin value and the *AUC* decreased significantly. The timing of the highest cholecystokinin level tended to shift towards an earlier occurrence.

Table 2. Values of the different treatment groups before (T_1) and 1 month after (T_2) randomization. Data are given as the mean ± standard deviation

	Placebo		60 mg orlistat		120 mg orlistat	
	T_1	T_2	T_1	T_2	T_1	T_2
n	12	12	14	14	14	14
Body weight (kg)	110.5 ± 16.8	109.4 ± 16.3*	107.5 ± 13.3	105.9 ± 13.1‡	102.6 ± 12.3	100.1 ± 12.6‡
Body mass index (kg/m^2)	37.8 ± 3.7	37.4 ± 3.8	36.6 ± 4.2	36.0 ± 4.0‡	35.7 ± 3.8	34.9 ± 3.9‡
Fasting volume (mL)	31.0 ± 10.5	25.9 ± 6.2	30.5 ± 13.8	37.3 ± 18.0*	21.1 ± 8.8	29.8 ± 12.4†
Residual volume (mL after 90 min)	10.1 ± 6.8	8.7 ± 6.9	12.7 ± 8.4	15.7 ± 10.4	7.4 ± 6.4	12.3 ± 8.2
Gall-bladder emptying (%)	69.1 ± 14.6	66.4 ± 25.2	59.0 ± 16.4	59.7 ± 16.5	64.8 ± 24.2	59.6 ± 17.9
Ejection volume (mL)	21.0 ± 7.2	17.2 ± 7.9	17.8 ± 8.9	21.6 ± 10.9	13.8 ± 7.9	17.5 ± 8.1
AUC gall-bladder (mL.90 min)	2049.6 ± 1112.8	1702.8 ± 680.0	2199.7 ± 992.0	2428.5 ± 1236.9	1408.5 ± 663.8	2017.1 ± 986.0*
Fasting CCK (pM)	1.29 ± 0.58	1.03 ± 0.50	1.56 ± 0.93	1.16 ± 0.62	1.59 ± 0.70	1.06 ± 0.45*
Peak CCK (pM)	2.91 ± 0.96	2.48 ± 1.04	3.06 ± 1.39	2.64 ± 0.95	2.97 ± 1.19	2.52 ± 0.82
Time of peak CCK (min)	45.0 ± 14.3	43.8 ± 16.3	38.6 ± 15.3	33.2 ± 13.4	46.1 ± 11.0	40.7 ± 16.0
Incremental CCK (pM)	1.62 ± 0.52	1.45 ± 0.91	1.51 ± 0.73	1.48 ± 0.60	1.38 ± 1.07	1.46 ± 0.68
AUC CCK (pM.60 min)	148.6 ± 54.4	125.4 ± 57.6	167.4 ± 78.2	140.1 ± 55.3	159.2 ± 48.2	124.7 ± 40.3*
Energy (MJ)	5.6 ± 1.1	5.9 ± 1.1	6.0 ± 1.5	6.5 ± 1.5	5.8 ± 1.7	5.6 ± 2.1
Fat (g)	49.3 ± 13.5	49.2 ± 12.9	52.5 ± 16.7	54.0 ± 12.9	49.6 ± 22.1	45.5 ± 23.2
Fat as percentage of total energy	33.4 ± 8.1	31.5 ± 4.7	33.5 ± 6.7	31.7 ± 4.4	31.5 ± 5.0	29.2 ± 6.9

AUC, area under the curve; CCK, cholecystokinin.
* $P < 0.05$.
† $P < 0.01$.
‡ $P < 0.001$.

Effect of 1-month treatment with lipase inhibitors (Table 2) — inter-group comparison. When comparing the three groups, values at the start were not different, except for a significant trend (ANOVA; $P = 0.047$) in the fasting gall-bladder volume, which decreased in the order placebo, 60 mg orlistat and 120 mg orlistat. The absolute values were not different. To correct for this difference at the start, proportional changes were investigated. Proportional changes in the fasting gall-bladder volume showed a significant difference between the three groups: an 11.2% decrease in fasting volume in the placebo group, a 25.9% increase in the 60 mg orlistat group and a 47.4% increase in the 120 mg orlistat group. In addition, proportional changes in the *AUC* were different and decreased by 9.4% in the placebo group and increased by 15.0% and 52.8% in the 60 mg and 120 mg orlistat groups, respectively. The difference was significant between the placebo and 120 mg orlistat groups.

When orlistat-treated patients as a group were compared with placebo-treated subjects, the values before randomization were similar, but differed after 1 month of treatment: the fasting volume and *AUC* were a mean of 47.8 ± 12.7% and 43.3 ± 17.1% higher, respectively, in orlistat-treated patients.

At the start and after 1 month of treatment, the basal, highest and incremental cholecystokinin levels and *AUC* were no different in the three groups. In addition, there was no difference in compliance with the ingestion of orlistat (pill counts) or diet (with respect to energy and fat intake, as reported in the diaries) between the groups.

Effect of 1-year treatment with lipase inhibitors (Table 3) — intra-group comparison. After 1 year of treatment, placebo patients lost a mean ± S.E.M. of 7.9 ± 3.0 kg. The trend of improving gall-bladder kinetics (decreasing fasting and residual gall-bladder volumes, decreasing gall-bladder *AUC* and increasing gall-bladder emptying) was abolished after 1 year.

Treatment with 60 mg orlistat resulted in a weight loss of 6.9 ± 2.0 kg. The insignificantly increased fasting, residual and ejection volumes at 1 month remained after 1 year. In addition, gall-bladder emptying remained delayed as shown by the percentage of emptying and *AUC*.

In 120 mg orlistat-treated subjects, a weight loss of 9.1 ± 1.4 kg was observed. The significantly higher fasting volumes after 1 month remained significantly higher after 1 year. The residual and ejection volumes stabilized at the higher levels reached after 1 month. In addition, the disturbed emptying (percentage of gall-bladder emptying and *AUC*) remained. A significant time effect was seen in fasting and residual volumes and in the *AUC* of the gall-bladder.

When considering patients treated with orlistat as a group, fasting and residual gall-bladder volumes were significantly higher at T_3 (6.5 ± 1.8 and 3.7 ± 1.7 mL, respectively) when compared with T_1, after a weight loss of 7.9 ± 1.2 kg. In addition, the *AUC* was higher (406.3 ± 174.7 mL.90 min). The time trends for these parameters were significant.

When looking at the cholecystokinin values, the lower values found at T_2 tended to recover in the months thereafter in the three groups. Only the incremental cholecystokinin value appeared to decline further in both groups of orlistat-treated subjects. In the 120 mg orlistat group, the peak value of cholecystokinin occurred 17.3 ± 6.3 min earlier when T_1 was compared with T_3.

When orlistat-treated subjects as a group were pairwise compared in time, the fasting values of cholecystokinin increased significantly between T_2 and T_3 (0.5 ± 0.2 pM), but this did not result in different values when T_1 and T_3 were compared.

Effect of 1-year treatment with lipase inhibitors (Table 3) — inter-group comparison. The values at the start for the three groups were not different. Comparison of the three groups showed that the significant proportional changes in fasting gall-bladder volumes and *AUC* in the first month between placebo and 120 mg orlistat-treated subjects did not persist. After 1 year, there were no differences between the groups, not even when all orlistat-treated subjects were compared with subjects on placebo.

Comparison of the three groups showed a difference only in the time to the peak value of cholecystokinin, which was significantly earlier in 120 mg orlistat-treated patients. A similar result was found when all orlistat-treated patients were compared with placebo-treated subjects.

The influence of body weight and body weight loss

At randomization, body weight was not related to gall-bladder kinetics or cholecystokinin values. After 4 weeks, incremental cholecystokinin values were inversely related ($r = -0.315$, $P = 0.047$) to body

Table 3. Analysis of gall-bladder kinetics and cholecystokinin (CCK) values (mean ± standard deviation) before (T_1) and 1 month (T_2) and 1 year (T_3) after randomization to placebo, 3 × 60 mg orlistat and 3 × 120 mg orlistat

	T_1	T_2	T_3
Placebo (*n*)	9	9	9
Body weight (kg)	106.1 ± 12.7	105.3 ± 12.6(§)	98.2 ± 16.9(††)
Fasting volume (mL)	33.2 ± 9.9	27.1 ± 6.1	32.1 ± 13.5
Residual volume (mL after 90 min)	10.7 ± 7.7(*)	7.6 ± 5.8	14.8 ± 11.1
Gall-bladder emptying (%)	70.2 ± 16.4	72.8 ± 20.3(§)	56.2 ± 26.3
Ejection volume (mL)	22.5 ± 6.4	19.6 ± 6.8	17.3 ± 9.7
AUC gall-bladder (mL.90 min)	2182.6 ± 1235.0	1719.8 ± 682.2	2277.8 ± 1190.0
CCK basal value (pM/L)	1.23 ± 0.57	1.02 ± 0.54	1.57 ± 0.80
CCK peak value (pM/L)	2.96 ± 1.02	2.46 ± 1.01	3.13 ± 1.38
Time of peak value (min)	43.3 ± 15.8	43.3 ± 13.9	48.3 ± 12.5
Incremental CCK (pM)	1.73 ± 0.56	1.43 ± 0.90	1.57 ± 0.69
AUC CCK (pM.60 min)	146.9 ± 55.5	125.0 ± 53.6	174.6 ± 88.2
Energy (MJ)	5.6 ± 1.6	5.6 ± 2.0	5.1 ± 2.0
Fat (g)	48.4 ± 22.7	46.4 ± 22.9	40.3 ± 23.2
60 mg orlistat (*n*)	12	12	12
Body weight (kg)	104.2 ± 10.7‡	102.5 ± 10.4(§)	97.4 ± 15.5‡‡
Fasting volume (mL)	29.3 ± 14.5	34.6 ± 17.8	33.5 ± 11.7
Residual volume (mL after 90 min)	11.8 ± 8.0	14.9 ± 10.9	14.4 ± 8.9
Gall-bladder emptying (%)	61.1 ± 11.2	59.7 ± 16.7	58.3 ± 20.7
Ejection volume (mL)	17.5 ± 7.7	19.7 ± 9.1	19.1 ± 7.8
AUC gall-bladder (mL.90 min)	2057.3 ± 1001.7	2251.4 ± 1251.9	2265.4 ± 861.6
CCK basal value (pM/L)	1.60 ± 0.99	1.17 ± 0.63	1.70 ± 0.87
CCK peak value (pM/L)	3.27 ± 1.39	2.67 ± 1.02	2.97 ± 1.30
Time of peak value (min)	37.5 ± 16.3	32.5 ± 14.1	37.5 ± 15.0
Incremental CCK (pM)	1.66 ± 0.66	1.50 ± 0.62	1.27 ± 1.07
AUC CCK (pM.60 min)	176.9 ± 79.6	142.1 ± 59.3	163.1 ± 64.88
Energy (MJ)	5.8 ± 1.6	6.3 ± 1.2	6.5 ± 1.8
Fat (g)	50.2 ± 17.0	53.0 ± 11.9	56.1 ± 18.5
120 mg orlistat (*n*)	11	11	11
Body weight (kg)	101.8 ± 13.4‡	99.1 ± 13.7**	92.7 ± 14.9§§
Fasting volume (mL)	22.1 ± 9.4†	30.8 ± 11.5	31.2 ± 11.8‡‡
Residual volume (mL after 90 min)	8.1 ± 7.1	12.3 ± 7.6	13.2 ± 9.1
Gall-bladder emptying (%)	62.6 ± 27.0	60.4 ± 18.9	59.5 ± 18.4
Ejection volume (mL)	14.0 ± 8.7	18.6 ± 8.4	18.0 ± 8.4
AUC gall-bladder (mL.90 min)	1502.4 ± 708.2*	2055.9 ± 918.5	2124.9 ± 1002.3
CCK basal value (pM/L)	1.61 ± 0.72(*)	1.00 ± 0.38	1.44 ± 1.17
CCK peak value (pM/L)	3.09 ± 1.33	2.52 ± 0.88	2.66 ± 1.49
Time of peak value (min)	47.7 ± 11.3	43.6 ± 15. 7	30.0 ± 16.4(††)
Incremental CCK (pM)	1.48 ± 1.17	1.52 ± 0.76	1.23 ± 0.86
AUC CCK (pM.60 min)	163.8 ± 53.0(*)	119.2 ± 36.4	138.3 ± 93.8
Energy (MJ)	5.6 ± 1.2	5.6 ± 1.0	5.3 ± 2.2
Fat (g)	47.4 ± 14.3	46.2 ± 12.5	41.9 ± 21.8

AUC, area under the curve.
* $P < 0.05$, † $P < 0.01$, ‡ $P < 0.001$ in comparison of T_1 with T_2.
§ $P < 0.05$, ** $P < 0.001$ in comparison of T_2 with T_3.
†† $P < 0.05$, ‡‡ $P < 0.01$, §§ $P < 0.001$ in comparison of T_1 with T_3.
(*), (§), (††): P values not significant because of multiple comparison (P by definition < 0.016).

weight. After 52 weeks, the residual volume ($r = 0.423$, $P = 0.016$) and gall-bladder *AUC* ($r = 0.360$, $P = 0.043$) were positively related to body weight and the percentage of gall-bladder emptying ($r = -0.414$, $P = 0.018$) was inversely related to body weight.

When looking at weight losses, no effects were found in the whole group after 4 weeks, but the percentage of

gall-bladder emptying was related to the absolute ($r = 0.361$, $P = 0.042$) and relative ($r = 0.359$, $P = 0.0430$) weight changes after 1 year.

A body weight loss of 10% of the initial weight was defined as a beneficial result after 1 year. When comparing the 21 subjects (three males and 18 females) who did not achieve this goal with the 11 (three males and eight females) who reached a weight loss of 10% or more, there were no differences at randomization in the starting weight, body mass index or food intake, nor in the absolute values of gall-bladder emptying and cholecystokinin, except for a fasting cholecystokinin value that was slightly higher (0.83 ± 0.26 pM) in the successful group. No independent effect of weight loss on gall-bladder and cholecystokinin values after 1 year could be established, despite differences of 11.4 ± 1.5 kg in weight loss and 4.5 ± 0.5 loss in body mass index units between the two groups, because of an interaction with treatment allocation.

Gallstone formation

Three patients appeared to develop gallstones after 1 year. One patient, randomized to 60 mg orlistat, initially lost 7.2 kg (5.7% of the initial weight), but regained all the lost weight after 1 year when the gallstones were discovered. Two patients, both on placebo, lost 15.0 kg (13.3%) and 21.9 kg (24.4%) over 52 weeks. One month after randomization, these three patients showed a significant 23.4% increase in the *AUC* of gall-bladder emptying, a significant 2.4-fold lowered fasting cholecystokinin value and a 1.3-fold decreased value of the *AUC* of cholecystokinin release, corresponding to delayed gall-bladder emptying and disturbed cholecystokinin release.

DISCUSSION

In the present study, adherence to an energy- and fat-restricted diet had no effects on gall-bladder kinetics and cholecystokinin release. This was expected because the intake of fat was well above the minimally required threshold of 10 g for gall-bladder emptying and 25 g for maximal gall-bladder contraction.[51, 52] One month of lipase inhibition, however, resulted in a significantly enlarged fasting gall-bladder volume in both the 60 and 120 mg orlistat-treated groups when compared with placebo. In the 120 mg arm, gall-bladder emptying was also significantly reduced, as was the fasting cholecystokinin value and the cholecystokinin release in response to a fatty meal. These findings fit our hypothesis that a diminution of free fatty acids in the intestinal lumen, in the gastric phase by inhibition of gastric lipase and in the intestinal phase by inhibition of pancreatic lipase, decreases cholecystokinin release and impairs gall-bladder contractility. Our data contrast with those of Froehlich *et al.*, who found no influence of a once-only 200 mg dose of orlistat on gall-bladder emptying and cholecystokinin release.[53] They argued that lipid malabsorption and steatorrhoea of 36%, induced by orlistat, would still leave behind 17 g of the 25 g of ingested triglycerides, enough to stimulate gall-bladder emptying. Borovicka *et al.*, however, demonstrated a lipase inhibition of 75% by 120 mg orlistat and, as a result thereof, impaired cholecystokinin release and gall-bladder emptying.[54] The disparate findings of Froehlich *et al.* may be explained by the low volume and low calorie content of the test meals used and the *in vitro* mixing of orlistat with the meal, presumably resulting in an insufficient lipase inhibition by orlistat. Our results agree with others with regard to cholecystokinin release and gall-bladder emptying.[54–57] Interestingly, our results of increasing inhibition by 120 mg orlistat than 60 mg orlistat confirm the findings of Hildebrand *et al.*, who found increasing inhibition of cholecystokinin release and gall-bladder emptying with increasing dosages of orlistat of 30, 60 and 120 mg, dosages that were shown to increase the fat excretion above basal values with 11.5 g, 15.4 g and 18.5 g, respectively.[44, 45, 57]

All the studies mentioned above investigated the effects of a once-only dose of orlistat, except for Borovicka *et al.*, who performed their investigations after a 4-day period of intake of 3000 kcal, with 31% of energy coming from fats, and a 4-day period of a daily intake of 3×120 mg orlistat.[54–57] Gall-bladder motility has also been examined after 4 weeks of either 120 mg orlistat t.d.s. or placebo in conjunction with a 1200–1500 kcal hypocaloric diet.[58] No changes were noticed, although it is unclear whether the subjects took the drug before the ingestion of the standardized meal. After 4 weeks, adverse changes in total bile acid and phospholipid concentrations were only observed in the placebo group, leading the authors to speculate that the risk of stone formation might actually be lowered with orlistat.[58]

Our study dealt with both the short-term and long-term effects of orlistat and with diets moderately

restricted in energy and fat, and thus mirrors more closely the normal clinical situation. After 1 year of orlistat treatment, some of the unfavourable conditions with regard to gall-bladder emptying persisted, but the cholecystokinin release recovered to some extent, resulting in an overall persistent but attenuated effect of orlistat on gall-bladder emptying and cholecystokinin release after 1 year.

The question of how much impaired gall-bladder emptying is clinically relevant and will lead to gallstone formation remains unresolved. In our study, three patients appeared to develop gallstones after 1 year, one with no weight loss on 60 mg orlistat and two on placebo with weight losses that were below 1.5 kg/week, but almost equal to (22.6%) or above (37.1%) the 24% initial body weight loss often quoted to represent a considerable risk of gallstone formation.[18, 20, 22] They showed disturbed cholecystokinin release and decreased gall-bladder motility 1 month after randomization. Unfortunately, there was no gall-bladder emptying study in between 1 month and 1 year and, after the discovery of the asymptomatic gallstones, these three patients were excluded from the gall-bladder study.

A search of all published orlistat studies since 1993 revealed 24 reports, but only in six studies were multiple gallstones or symptomatic gallstones mentioned as exclusion criteria.[45, 59–63] Five of these studies included ultrasounds of the kidney and gall-bladder at the start and at completion of the study,[45, 59, 61–63] because of the fear of gallstones and oxalate kidney stones. Four studies reported no evidence of increased stone formation.[45, 59, 61, 62] Only one study gave figures: mostly asymptomatic stones in 11% of placebo-treated subjects and in 7% of orlistat-treated subjects after 1 year.[61] Our 1-year results in a much smaller group showed 16.7% gallstone development in placebo-treated patients and 7.1% in 60 mg orlistat-treated patients, with no stone formation in the 120 mg orlistat-treated group. These data do not support an excess risk because of lipase inhibition in uncomplicated obesity.

However, the findings of disturbed gall-bladder emptying and cholecystokinin release after 1 month of orlistat treatment, which were attenuated to some extent after 1 year, indicate that larger and longer trials are necessary to exclude possible adverse effects. In particular, disturbed gall-bladder emptying with 120 mg orlistat t.d.s., which is the recommended intake, should be further investigated in complicated obesity, i.e. in obese subjects more at risk of gallstone formation because of diabetes or hyperlipidaemia.

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