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An assessment of the efficacy and safety of orlistat for the long-term management of obesity

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Pancreatic and gastric lipases hydrolyze dietary triglycerides into 2-monoacylglycerols and free fatty acids prior to systemic absorption. Orlistat, a potent gastrointestinal lipase inhibitor, is undergoing review by the Food and Drug Administration as a new treatment for obesity. When given with a fat-containing meal, orlistat 120 mg three times a day reduces fat absorption by approximately 30%, which equates to a decrease in caloric absorption of approximately 200 kcal/d. A 2 year European study found that 75% of obese subjects on low-fat, energy-deficient diets plus orlistat lost and maintained a modest but medically significant amount of weight. The loss was twice as high as that of subjects taking placebo. Side effects in individuals taking the drug, which were related to orlistat's mechanism of action, included oily spotting, flatulence, and frequent loose stools. Patients did not experience frank diarrhea or intestinal malabsorption. Vitamin D and β-carotene levels decreased but remained within the normal range. In summary, orlistat is the first example of a new class of antiobesity drugs that interferes with dietary fat absorption, enhances weight loss and weight maintenance, has tolerable gastrointestinal side effects, and has no major drug toxicity. Orlistat may prove to be useful in clinical practice as an adjunct to nonpharmacological weight management interventions, particularly low-fat energy-deficient diets. (J. Nutr. Biochem. 9:516–521, 1998) © *Elsevier Science Inc. 1998*

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Introduction

There is evidence that diets high in fat promote the development and maintenance of obesity (see Golay and Bobbioni[1] for a review). The majority of population-based studies have demonstrated a relationship between dietary fat intake and obesity: countries with the highest fat intake have the highest prevalence of obesity.[2,3] In the Vermont overfeeding study, lean prison volunteers receiving dietary fat supplements gained weight more readily and required less dietary energy to maintain the elevated weight than did volunteers overeating a mixed meal of carbohydrates and fat.[4] In taste response studies, obese subjects showed a preference for higher fat foods than lean subjects.[5] The proposed mechanisms for the obesity-promoting effects of dietary fat are: (1) fat has a high caloric density that encourages overconsumption, (2) the metabolic cost of storing dietary fat is less than that of carbohydrates and protein, and (3) dietary fats are less thermogenic than the other macronutrients.[6,7] Collectively, the aforementioned studies and others have led to recommendations to limit dietary fat intake during energy-restricted weight reduction. Conservative strategies to limit fat intake have focused on dietary education. However, despite a heightened awareness of the health risks of dietary fat, the long-term commitment to a rigorous diet therapy plan is problematic for most obese patients.

To circumvent the difficulties of dieting, several nutritional products have been developed. Fat substitutes such as olestra are one such product designed to limit dietary fat intake. Olestra is a large molecule made from vegetable oil and sucrose that is designed to taste and feel like fat but

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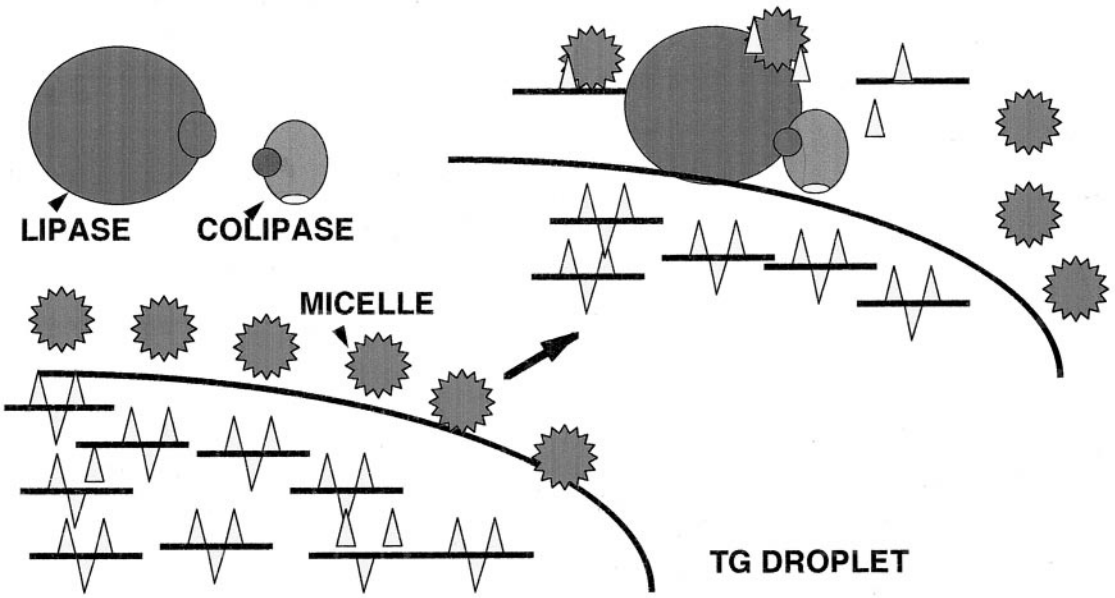

Figure 1 Triglyceride digestion mediated by pancreatic lipase and colipase.

provide none of the calories because it is not absorbed.[8] Foods containing olestra are restricted by law to snack food such as potato chips and crackers. Thus, the ability to make a global change in dietary fat intake based solely on olestra is limited. The intake of olestra can have some side effects. Adults eating an excess of olestra-containing products (the average is 5 snacks in 14 days) develop abdominal cramping and loose stools.[9] These side effects are thought to be related to the presence of an excess amount of the nonabsorbed product in the gastrointestinal tract. The second tactic to limit dietary fat intake involves the replacement of products that are traditionally high in fat with low-fat or fat-free forms. This tactic is also problematic: consumers overeat these low-fat products with the idea that they will not gain weight, but the opposite has occurred.[10]

Now a new class of pharmacological agents has been developed that limits dietary fat by inhibiting fat digestion. Orlistat is the first drug of this class to be tested in clinical trials and to undergo review by the Food and Drug Administration (FDA). The purpose of this article is to examine the preclinical and clinical efficacy and safety data of orlistat under the premise that this drug may soon be available for the long-term treatment of obesity.

Dietary fat intake and metabolism

In western countries, the average intake of dietary fat constitutes approximately 36% of total daily caloric intake.[10] Current dietary guidelines recommend limiting dietary fat intake to less than 30% of total daily caloric intake.[11] Triglycerides account for more than 95% of the 50 to 120 g of lipid consumed per day by the average adult in affluent cultures.[12] Other dietary lipids include phospholipid (2–4 g/d) and cholesterol (250–600 mg/d). Dietary triglycerides must undergo a series of gastrointestinal degradation processes before they are absorbed from the small intestine into the bloodstream (*Figure 1*). The steps for triglyceride digestion require emulsification, hydrolysis of the fatty acid ester linkage by lipases, aqueous dispersion of lipolytic products in bile acid/phospholipid micelles, absorption and reesterification by the upper jejunum, and secretion into the circulation in the form of chylomicrons.[13] Lipase-mediated hydrolysis of dietary triglyceride is the key step in lipid digestion. Four main lipases have been identified in humans that are involved in lipid digestion: gastric lipase, pancreatic lipase, carboxylester lipase, and phospholipase A_2 (PLA_2). Gastric lipase degrades only about 10 to 20% of dietary fat in the stomach but stimulates pancreatic lipase activation. Pancreatic lipase, in conjunction with a pancreatic colipase, is the primary enzyme responsible for the digestion of dietary triglyceride. It is secreted from the pancreas into the duodenum in response to emulsified lipids entering the duodenum. Patients with congenital pancreatic lipase or colipase deficiency absorb approximately 50% of their dietary fat, in contrast to the more than 90% absorbed by normal individuals.[14] Carboxylester lipase from the pancreas plays a minor role in triglyceride and vitamin ester hydrolysis but has greater significance in triglyceride degradation in people with exocrine pancreatic insufficiency.[15,16] PLA_2 from the pancreas functions to hydrolyze phospholipids in the presence of calcium and bile salts.[13]

Pharmacology

Orlistat (tetrahydrolipstatin) is a semisynthetic hydrogenated derivative of a naturally occurring lipase inhibitor produced by *Streptomyces toxytricini*.[17,18] Structurally it contains an aliphatic hydrocarbon backbone, with a β-lactone functional group and an N-formyl-L-leucyl ester side chain (*Figure 2*). Orlistat is a potent inhibitor of gastric, carboxylester, and pancreatic lipases both in vitro and in vivo. The effect of orlistat on pancreatic lipase has been best

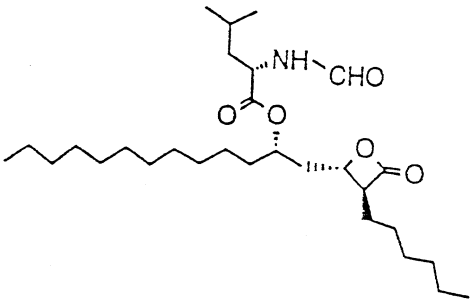

Figure 2 Chemical structure of orlistat.

studied. The pancreatic lipase recognizes orlistat as a substrate. The lipase and inhibitor form a stable, slowly degrading drug–enzyme complex that induces the opening of a lid-like structure on the lipase, thereby exposing the catalytic site. This conformational change leads to acylation of a hydroxyl group on the active site serine residue and inactivation of the enzyme.[19] Unhydrolyzed dietary triglycerides pass through the intestine and ultimately into the feces.

Orlistat is minimally absorbed into the systemic circulation. After a single dose (360 mg) of radiolabeled orlistat, 1% was recovered in the urine and 96% in the stool.[20] Of the small amount of drug reaching the circulation, there are two main metabolites (M1 and M3) that account for 42% of the total metabolized drug. The half-life of M1 is approximately 2 hr, and M3 slightly slower. All of the metabolites of orlistat are thought to be inactive, since the opening of the β-lactone ring occurs as an early step in metabolism of the drug and renders the drug inactive. The kinetics of the drug are similar in obese and lean healthy volunteers.

Drug–drug interaction studies were performed with orlistat and drugs with a narrow therapeutic window or with medications commonly taken by obese patients. Orlistat between 80 and 120 mg t.i.d., given for 4 to 8 days, had no significant effect on the pharmacokinetics of a single dose of atenolol, captopril, furosemide, nifedipine XL, warfarin, phenytoin, digoxin, or glyburide (*Table 1*).[21–26] The anovulatory properties of oral contraceptives were not altered by orlistat.[27] In contrast, orlistat increased pravastatin levels by 26 to 33%, enhanced its lipid lowering properties, and had no effect on its plasma elimination half-life.[28] Whether these short-term interactions will be similar with long-term use of orlistat remains to be seen.

Table 1 Orlistat has no effect on the pharmacokinetics of a single dose of these drugs

Atenolol	Nifedipine XL
Captopril	Oral contraceptive
Digoxin	Phenytoin
Glyburide	Warfarin
Lasix	

Mechanism of action

Experimental animal studies

Two studies in rats assessed the effect of orlistat on body weight and food intake. In the first study, 70-day-old rats were fed moderately high fat diets (14.5% fat) for 17 weeks to induce obesity.[29] The diet-induced obese rats, which weighed 818 ± 13 g, were given either orlistat or placebo for 22 days. Both groups were maintained on the same moderately high fat diet during the treatment period. The orlistat treated group lost 65 ± 8 g of body weight, while the control group gained 9 ± 5 g of body weight. Food intake increased 9% in the orlistat treated group, but remained stable in the control group. These results suggested that orlistat mediated weight reduction through inhibition of dietary fat absorption, not through decreased food consumption.

The second study examined macronutrient preference in 80-day-old lean rats treated with either orlistat or placebo.[30] Three different sources of macronutrients were simultaneously provided to the animals in different vessels for the rats to self-select, ad libitum: 90% protein, 91% carbohydrate, and 86% fat. Orlistat significantly attenuated normal growth, but did not cause weight loss. Rats treated with orlistat became hyperphagic, primarily from increased carbohydrate and protein intake. The investigators also found no measurable aversion to the fat diet when orlistat was added. The main conclusions from these experiments suggested that orlistat limits fat digestion by decreasing both fat intake and fat absorption, but at the expense of increasing the caloric intake of other macronutrients. One possible explanation for the apparent discrepancy between the two studies is that in the second study, the rats were able to self-select the macronutrient composition of their diet, given a choice of carbohydrate, protein, or fat sources of nutrients. In the former study, only the moderately high fat meal was provided. In addition, the rats were obese in the former study and lean in the latter. It is possible that lean and obese animals adjust their macronutrient intake differently in response to orlistat. Similar studies have not been reported in lean and obese humans.

Clinical studies

In healthy lean humans orlistat at low doses (80 mg t.i.d) decreased dietary fat absorption by 10 to 20%. Orlistat at higher doses (100, 200, and 400 t.i.d) decreased fat absorption by 25 to 35%.[31] Doses above 400 mg/d did not increase fat excretion by more than 35%. The amount of fat excreted varied directly with the amount of fat ingested. The threshold for fat excretion may be due to a temporal difference in the rate that orlistat and fat enter the duodenum. Fat may remain in the stomach for several hours after the meal, while orlistat is thought to leave the stomach earlier together with gastric juices and water.[32] Arguing against this hypothesis, orlistat was equally effective in inhibiting fat absorption when administered midmeal, 1 hr, or 2 hr after a meal.[33] Another question posed was whether orlistat inhibited dietary fat digestion when the fat was presented as an integral part of other foods, meats, or dairy products. Orlistat was equally effective in inhibiting fat absorption

from oils or whole food sources.[34] High amounts of dietary fiber did not interfere with orlistat's inhibitory properties.

Antiobesity effects of orlistat

Several short-term studies demonstrated that orlistat and energy-restricted diets induced weight loss of approximately 0.25 to 0.5 kg/week.[35,36] For example, in a 12-week, double-blind, randomized, placebo-controlled trial, subjects were placed on a restricted diet (500 cal/d deficit) with or without orlistat. The predicted weight loss was estimated to be 5 kg in the placebo group based on the initial calculation and food records. The placebo group lost 3.4 kg, and the orlistat group 4.7 kg. These results suggested that either the initial calculation was inaccurate or that the subjects in the placebo group were underreporting their food intake. The fact that the orlistat group lost about what was predicted indicates that the drug is not synergistic with or additive to the diet effect. However, these short-term studies demonstrating that orlistat was better than placebo prompted additional studies to determine whether the effect on weight loss could be sustained for 1 to 2 years.

A report of a 1 year randomized, double-blind, placebo-controlled trial of 46 obese men and women from a single site determined the effect of orlistat 120 mg t.i.d. on weight loss.[37] Subjects were placed on a 600 kcal energy deficit diet containing 30% fat and less than 10% saturated fat. Caloric intake was decreased further at 24 weeks by 300 kcal. Using the intention-to-treat analysis, most of the weight loss occurred during the first 6 months of the trial in both the orlistat (8.4%) and placebo groups (5.7%). At 52 weeks, subjects in the orlistat group maintained all of their initial weight loss, but the placebo group regained all but 2.6% of their initial weight loss, despite lowering the caloric intake further at 24 weeks. Although the amount of weight loss was relatively small in both groups, other studies have demonstrated clear health benefits from small amounts of weight loss.[38] Preliminary results of a 2 year randomized, double-blind, placebo-controlled trial reported that approximately 75% of subjects on orlistat 120 mg t.i.d achieved a modest amount of weight loss (10% of initial body weight).[39] The conclusions from this study were that orlistat is effective in producing and maintaining modest weight loss over a 2 year period. Results from the 2 year study including U.S. sites have not been published.

Secondary effects of orlistat

Lipids

Development of an antiobesity drug with beneficial effects on serum lipids is desirable because obesity and hyperlipidemia frequently coexist. Intestinal free fatty acids increase the solubility of dietary cholesterol and enhance its absorption.[40] Because of its inhibitory effects on the liberation of intestinal fatty acids, orlistat was examined for its cholesterol lowering properties. In a multicenter, randomized, double-blind study of 103 men and 70 women [body mass index (BMI) >19 and <28.7 kg/m^2), respectively] orlistat 120 mg t.i.d. given for 8 weeks lowered total cholesterol 11% and low-density lipoprotein (LDL) cholesterol 10%.[41] High-density lipoprotein (HDL) decreased slightly, but this finding is not uncommon during early stages of weight loss. Subjects lost an average of 1.2 kg, despite a weight maintenance diet. In the 12 week efficacy study, normolipidemic subjects had a decrease in total and LDL cholesterol, but not in triglycerides or HDL.[35] At the end of the 1 year efficacy study, the placebo group had increased total and LDL cholesterol 9.7% and 4.8%, respectively,[37] whereas the orlistat group showed no change in total cholesterol and a 4.2% decrease in LDL cholesterol. HDL showed little change in either group. There are no published reports on the effect of orlistat on lipid levels in obese hyperlipidemic subjects. When published, the results from the 2 year studies, with a larger number of subjects, may better define orlistat's lipid lowering potential.

Blood pressure

In the 1 year efficacy trial, the effect of orlistat on blood pressure was examined.[37] Blood pressures obtained after the 4 week diet control period were used as a baseline (rather than blood pressures at entry) and were compared with the blood pressures obtained after 52 weeks of treatment with orlistat or placebo. Diastolic blood pressure increased 2.2 ± 7.3 mmHg in the placebo group and 2.7 ± 6.8 in the orlistat group. The absence of an improvement in blood pressure after weight loss was not surprising because: (1) subjects lost weight during the initial diet control period and may have experienced an initial decrease in blood pressure during this period of time, and (2) the mean blood pressures in the study groups were normal at the beginning of the study.

Side effects

Gastrointestinal

Gastrointestinal symptoms are the most commonly reported side effects with orlistat. Approximately 10 to 30% of subjects on orlistat 360 mg/d reported increased defecation, soft stools, fatty oils evacuation, and oily spotting.[37] One or more gastrointestinal events were reported by 75% of subjects. These symptoms, although bothersome, were often transient and mild. Some investigators have proposed that these side effects serve as a powerful enforcer of the low fat diet because high fat intake worsened the gastrointestinal side effects.[32,37]

Cholecystokinin (CCK) is a key inducer of gallbladder contraction. CCK release is stimulated by increased levels of intestinal free fatty acids.[42] Because orlistat decreases intestinal free fatty acid formation, it is theoretically possible that orlistat also decreases CCK secretion. The decreased CCK might result in diminished meal-related contractions of the gallbladder and in the formation of gallstones. In six healthy nonobese subjects who consumed either a 100% fat, mixed, or fat-free meal, orlistat had no effect on gallbladder contraction or CCK levels in the blood.[43] Orlistat had no effect on stomach acidity, pancreatic secretion, or gastrointestinal transit time.

Table 2 Effect of orlistat on endogenous vitamin levels

Vitamin A (μmole/L)	Vitamin D (nmole/L)	β-carotene (μmole/L)	α-tocopherol (μmole/L)	α-tocopherol/chol	Vitamin K
no change	decrease[1]	decrease[1]	decrease	no change	no change

[1]Levels remained within normal limits.

Endogenous vitamin levels and absorption of supplemental vitamins

Another major question posed was whether orlistat interfered with the absorption of the lipid-soluble vitamins A, D, E, and K, and the provitamin β-carotene. Orlistat interferes with lipases that hydrolyze vitamin esters, particularly vitamins E and A.[15] Additionally, the increase in intestinal oil could potentially interfere with lipid-soluble vitamin absorption. In an 8 week study of orlistat, serum vitamin A and prothrombin time (vitamin K) were not affected by orlistat.[44] Serum vitamin E and 25-hydroxy vitamin D_3 concentrations decreased but remained within the normal range. The decrease in vitamin E was similar to the decrease in LDL, which is a principle carrier of vitamin E. In the 1 year study, serum levels of β-carotene and 25-hydroxy vitamin D_3 were decreased by orlistat, but reached and maintained a new steady-state before the end of the study[37] (*Table 2*). However, 6 of 23 subjects received lipid-soluble vitamin supplements after two consecutive blood vitamin levels were found to be below the reference range. It is not known whether these changes in serum levels reflect changes in tissue stores.

To address the issue of vitamin supplements, 12 healthy lean volunteers received vitamin A (25,000 IU) and vitamin E (400 IU) supplements.[44] Orlistat 120 t.i.d demonstrated no effect on vitamin A absorption, but decreased the maximum serum concentration 43% and the area under the curve 60% for vitamin E. A separate study showed that orlistat 120 t.i.d decreased absorption of supplemental β-carotene 120 mg by one third,[45] but no changes in endogenous levels of β-carotene occurred during the 6 days of administration of orlistat. The decreases seen in the serum concentrations of fat-soluble vitamins make it essential to develop guidelines for monitoring serum vitamin levels and for providing supplements should these serum concentrations fall below a certain level.

Serum hormone levels

Hormones such as thyroxine, catecholamines, and insulin-like growth factors (IGF) are altered by dietary changes.[46–48] In a study of the effect of orlistat 120 mg t.i.d., given for 12 weeks, on hormone status of seven moderately obese, nondiabetic men and women, orlistat had no effect on thyroid-stimulating hormone, Free T4, Free T3, reverse T3, epinephrine, norepinephrine, IGF-1, or IGFBP-3.[49] There was also no effect on serum glucose, triglyceride, or free fatty acids in these subjects.

Summary

Dietary fat may play a key role in the development of obesity. Novel strategies to limit dietary fat intake in obese individuals are being explored. The intestinal lipase inhibitor orlistat shows promise as a safe and effective adjunct to diet and exercise in the long-term management of obesity. Although initial clinical studies have generated some optimism, several practical and scientific issues warrant further study and discussion before the drug is widely used. First, will patients paying for the drug tolerate the gastrointestinal side effects for 10% weight loss? What kind of dietary education is needed to minimize gastrointestinal side effects? What are the long-term consequences, if any, of the decreases in serum levels of the lipid soluble vitamins and β-carotene? Does orlistat have appetite suppressing effects or effects on macronutrient intake? Are there any problems with drug–drug interactions in the long-term? Finally, what effect does the drug have on coexisting diseases in obese subjects, particularly diabetes, hyperlipidemia, and hypertension?

The intent of this review was to summarize the clinically relevant data on orlistat, to stimulate further scientific discussion, and to provide clinicians with background information that may help them and their patients make an informed decision regarding the use of orlistat if and when it reaches the U.S. market.

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