Is blockade of pancreatic lipase the answer?1,2

Charles H Halsted, Editor-in-Chief

Two original research communications and 2 editorials in this month’s issue of the Journal illustrate the dilemmas of the current treatment of obesity (1–4). The paper by Astrup et al (1) and editorial by Hill and Wyatt (2) teach us that the preponderance of obesity is most probably caused by a tipping of the energy equation toward excessive intake of energy rather than too little energy expenditure. The evidence surrounding this concept reinforces the notion that effective obesity therapy must be directed toward limiting the intake or absorption of dietary energy, whether through behavioral modification of eating habits, effective pharmaceutical suppression of appetite, or selective disruption of the normal processes of digestion. Whereas it is nearly axiomatic that behavioral modification is effective only for the few whose time, motivation, and financial resources permit intensive retraining in eating and exercise habits, and whereas anorectic drugs pose unacceptable or potential risks, the focus now turns to selective blockade of dietary fat absorption through inhibition of the pancreatic enzyme lipase.

Is orlistat effective? The recently published, large multicenter trial of 892 patients with body mass indexes (in kg/m²) ranging from 30 to 43 provides a qualified yes (5). In this study, patients who received the maximal dose (360 mg/d), sufficient to inhibit the digestion of 30% of dietary fat, achieved a mean weight loss of 8.7 kg (≈10% of initial weight) compared with a mean weight loss of 5.8 kg (≈7% of initial weight) in the placebo group during 1 y. Those who received the maximal orlistat dose for another year regained only 35% of their original weight compared with a regain of 63% of original weight in the placebo group. The study by Hill et al (3) showed that decreased body weight was sustained by 24% of patients taking the maximal dose of orlistat. Furthermore, fasting serum glucose and insulin concentrations, LDL-cholesterol concentrations, and blood pressure were significantly reduced in patients who took the maximal dose for 2 y (5).

Yet, can these results truly be considered a success in the treatment of obesity, a chronic disease that typically lasts a lifetime? One must question why after 1 y of treatment three-fourths of patients had begun the relentless process of weight regain despite continued orlistat therapy and whether, as in the placebo group, all early positive effects on weight reduction and metabolic changes were erased over time. One suspects that patients receiving orlistat undergo a form of behavioral adaptation by either out-eating the intent of the drug through increased consumption of dietary fat or by circumventing its effect through increased consumption of carbohydrate energy. Furthermore, one must evaluate these findings with the caveat that they were achieved in a highly structured clinical trial setting with frequent dietary counseling and physician contact—hardly the real world of obesity treatment for the one-third of Americans at risk.

Is orlistat safe? Although inconvenient abdominal symptoms such as increased flatus, oily stools, and fecal incontinence and urgency were reported by 10–40% of patients, these problems were substantially less frequent in the second year. Concentrations of the fat-soluble vitamins D and E were significantly reduced by 1 y of orlistat treatment, but low concentrations rose to normal with appropriate vitamin supplementation of deficient patients (5). Nevertheless, one must question whether chronic fat malabsorption and steatorrhea resulting from prolonged orlistat treatment has unforeseen yet potentially pathophysiological consequences. In a different clinical model, osteopenia and osteoporosis that were not correlated with vitamin D concentrations were documented by bone mineral density measurements in a group of patients with pancreatic insufficiency and steatorrhea due to chronic pancreatitis (6). Although other factors may contribute to metabolic bone disease in patients with chronic illness, this complication could be problematic in a largely peri- and postmenopausal population of women with drug-induced steatorrhea. These issues need to be assessed further in carefully controlled calcium balance studies and by bone mineral density measurements in long-term orlistat users.

Although some may consider this viewpoint overly pessimistic, the limited trial success with orlistat and the potential for unforeseen but plausible long-term consequences brings us back to the frustrating dilemma that there is as yet no predictably safe and effective long-term treatment for chronic obesity. Although reasonably based on our understanding of bioenergetics, the advice to eat less and exercise more works for only a few. Perhaps the cure for obesity can come only through the combination of radical public health changes in our sedentary fast-food culture and the development of creative applications based on a more detailed, molecular understanding of appetite and weight control in humans.

REFERENCES

1. Astrup A, Gøtzsche PC, van de Werken K, et al. Meta-analysis of...