INHIBITION OF GASTROINTESTINAL LIPOLYSIS BY ORLISTAT DURING DIGESTION OF TEST MEALS IN HEALTHY VOLUNTEERS.

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The lipase inhibitor Orlistat belongs to a new class of anti-obesity drugs. It prevents the lipolysis of dietary triglycerides (TG), and thus reduces the subsequent intestinal absorption of fat. In most clinical studies, the effects of Orlistat have been estimated indirectly from the fecal fat excretion levels, but the inhibition exerted on digestive lipases and the levels of lipolysis were not measured simultaneously in vivo.

The present clinical study provides the first comprehensive overview of test meal lipolysis by human gastric lipase (HGL) and pancreatic lipase (HPL) in healthy human volunteers, in the presence and absence of a lipase inhibitor. Orlistat was found to be a powerful HGL inhibitor, achieving 46.6 to 91.4 % enzyme inhibition and thus greatly reducing the gastric lipolysis of mixed solid/liquid and liquid meals (11 to 33 % of respective controls). The rate of HGL inhibition by Orlistat was extremely fast (half-inhibition time < 1 min). The effects of Orlistat on duodenal lipolysis were found to be more complex. The duodenal lipolysis was reduced significantly by Orlistat with the mixed solid/liquid meal (32.6 to 37.6 % of controls), but was only slightly reduced with the liquid meal (74.5 to 100 % of controls). The levels of HPL inhibition were found to be high (51.2 to 82.6 %) however, whatever the test meal. These paradoxical results were explained upon performing in vitro lipolysis experiments. The rates of HPL inhibition by Orlistat were found to be similar with both types of meals (half-inhibition time = 5-6 min), but the finely pre-emulsified TG of the liquid meal were rapidly hydrolyzed by HPL before the enzyme was significantly inhibited by Orlistat. With the mixed solid/liquid meal, the rate of hydrolysis of the meal TG by HPL was slower than the rate of HPL inhibition by Orlistat. As predicted from the previous results, the effects of Orlistat on the fat excretion levels were found to be much greater with the solid (40.5 to 57.4 % of ingested fat) than with the liquid test meal (4.2 to 18.8 %). This study therefore highlights the fact that lipase inhibition and lipolysis are two competitive processes which depend on the physico-chemical properties of the dietary TG.