

## Safety and Mechanism of Action of Orlistat (Tetrahydrolipstatin) as the First Local Antiobesity Drug

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**Abstract:** The benefits of orlistat, a new anti-obesity drug, have been assessed in this mini-review. The mechanism of action, as well as the clinical privilege of this peripheral acting drug on central acting drugs such as sibutramine, was discussed. Mono- and combined therapies for controlling the obesity are reported in short- and long-term therapy. Data were collected using MEDLINE search drug (June 1998-February 2005) using the terms: orlistat, sibutramine, obesity, overweight and antiobesity drug. Relevant references cited in the bibliography of related article also included were as possible. The search was not limited by language, gender or age, however only human sample has been considered. The aim of this review article is to assess the therapeutic efficacy of orlistat in glance.

**Key words:** orlistat, sibutramine, obesity, overweight, antiobesity drug

### INTRODUCTION

Obesity defined in West as a basal metabolic rate, body mass index (BMI)  $30 \text{ kg/m}^2$ , while Asian considered obesity when BMI  $25 \text{ kg/m}^2$ <sup>[1,2]</sup>. This disease associated with other prevalent diseases such as hyperlipidaemia, diabetes mellitus, hypertension, coronary heart disease, bowel cancer and cerebral stroke<sup>[1,2]</sup>. Thus, any treatment for controlling obesity will decrease the cost of health services. Obesity could affect anaesthesia procedure where high concentrations of anaesthetic drug accumulate in adipose tissue<sup>[3]</sup>. Postoperative complication may prevent some operations in obese patients such as hip replacement and aneurysm repair<sup>[3]</sup>. Overweight is often defined by lower BMI ( $25 \text{ kg/m}^2$  in West and  $23 \text{ kg/m}^2$  in East)<sup>[1,2]</sup>.

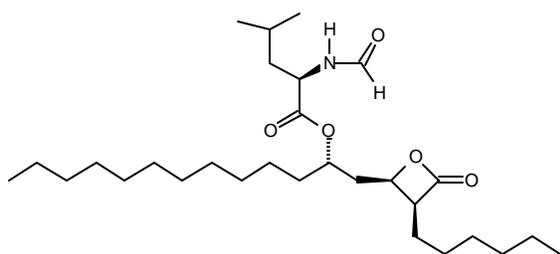
The available antiobesity agents have central effect with serious unwanted effect. Amphetamines have euphoric action and can lead to physiological and psychological addiction<sup>[4]</sup>. Phenylpropanolamine-containing agents<sup>[5]</sup>, fenfluramine and dexfenfluramine<sup>[6]</sup> all of which acting centrally as appetite suppressant via releasing serotonin. The Phenylpropanolamine-containing agents associated with increased risk of haemorrhage stroke especially in women while the last two compounds have been withdrawn from market due to their association with pulmonary hypertension and heart valves damage<sup>[4,5]</sup>. Phentermine interacts with catecholaminergic pathway leading to stimulant effect<sup>[4,6]</sup>. In contrast to the above compound, orlistat (tetrahydrolipstatin, Xenical<sup>®</sup> Fig.1) act peripherally at gastrointestinal tract and only 1% can

enter the circulation.

Roche Pharmaceutical Company has introduced orlistat at the end of 1998 in UK<sup>[7]</sup>. This drug received ample media coverage and represented as a magic medicine for obesity without pain of dieting. It is the first compound in a new pharmacological class that limits dietary fat absorption. Orlistat has been approved by the Food and Drug Administration (FDA) in 1999 for the weight-reduction in critical obesity conditions in conjunction with lifestyle modifications such as sport and low food intake<sup>[8]</sup>. The drug is licensed for patients with BMI  $>28 \text{ kg/m}^2$  but the decision should be based on the individual case. It is a semisynthetic hydrogenated derivative of naturally occurring lipase inhibitor produced by *Streptomyces toxytricini*<sup>[9,10]</sup>.

Orlistat is thought to have low abuse potential because it is not absorbed ( $<1\%$ ) and has no central effect. To date, only one case has been reported for the orlistat abused in average weight woman with eating disorder and stimulant dependence<sup>[11]</sup>. It inhibits potently and specifically the pancreatic lipase which is responsible, in conjunction with a pancreatic colipase, for the breakdown of dietary triglycerides into the absorbable fatty acids and monoglycerides<sup>[12]</sup>. This inhibition decrease the absorption of fats by  $>30\%$ <sup>[13]</sup>. In healthy human it leads to  $>90\%$  enzyme inhibition with no activity against trypsin, chymotrypsin, amylase, and phospholipases<sup>[14]</sup>. Orlistat also inhibits gastric lipase, carboxylester lipase, and phospholipase  $A_2$  that helps in lipid digestion both *in vitro* and *in vivo*<sup>[13,15,16]</sup>.

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**Fig.1:** Chemical structure of orlistat

**Mechanism of action and metabolism of orlistat:**

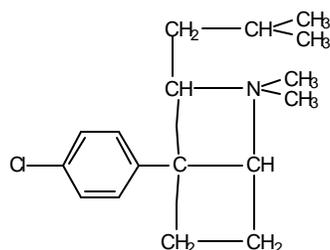
Orlistat binds covalently to the active site on pancreatic lipase and forms a stable complex<sup>[12]</sup>. The complex induces a conformational change in the enzyme that leads to a lid-like structure on the lipase, hence exposing the catalytic active site<sup>[17]</sup>. This operation leads to acylation of a hydroxyl group on serine residue burden on the active site of the enzyme making it inactive as lipase. The inactivated lipase is unable to hydrolyse fats into fatty acids and monoglycerides, which lead to their passage with faeces<sup>[17]</sup>.

Due to lipophilic nature of orlistat, it is minimally absorbed into circulation. After the ingestion of 360 mg radioactive orlistat, only 1% was found in urine and more than 96 % was recovered in stool over the following 4 days of administration. The half-life of this drug is 14-19 hr. This indicates that the drug is extensively excreted unchanged<sup>[18]</sup>.

Two metabolites are excreted via the bile have been detected, namely: M1 and M3. They found to be with no pharmacological activity in comparison to parent compound. The half-life of M1 and M3 are approximately 2hr and 3hr, respectively. M1 result from the opening of  $\beta$ -lactone moiety in orlistat while the M3 metabolite as a result of both the hydrolysis of  $\beta$ -lactone and ester group at the N-formyl leucine side chain (Fig.1). Orlistat was undetectable in plasma after 96 hr of administration of 400 mg t.i.d for 16 days, which may indicated the presence of extensive first-pass metabolism<sup>[18]</sup>.

**Clinical manifestations:** Orlistat decreases both lipids ingested and degradation and thus absorption. In lean humans orlistat decreases fat absorption by 20% and 35% when administered in low (80 mg t.i.d) and high (400 mg t.i.d) doses, respectively<sup>[19]</sup>. Higher doses did not decrease fat absorption above 35%, which supports the safety profile of the drug. However, the net amount of fat absorbed increase with increased fat intake. Studies demonstrated that orlistat administration with low calorie diet and exercise regimen decrease the weight by 0.5 kg/week<sup>[20]</sup>.

Combination therapy of orlistat and sibutramine (Fig. 2) is found to be more effective than orlistat mono-therapy and showed no superior action compare to



**Fig. 2:** Chemical structure of sibutramine

sibutramine mono-therapy<sup>[21]</sup>.

In long-term study, the benefits of orlistat treatment was assessed in 688 adult male and female obese patients (BMI 28-40 kg/m<sup>2</sup>) in single blind, placebo whose under a hypocaloric diet<sup>[22]</sup>. The volunteers received either placebo (n=343) or the drug (n=345, 120 mg t.i.d) for 52 weeks. After one year the patients with orlistat lost 10.25% of their weight. When the orlistat patients switch to placebo in the second year they regain 52% of their weight. That study indicated that combined orlistat with diet produces significant and clinically relevant reductions in weight in two years treatment<sup>[22]</sup>.

In multicenter studies consist of 2847 patients receiving orlistat with mild hypocaloric diet and a total of 1740 patients receiving placebo, a significant weight loss (p<0.05) with reduction in waist circumference has been noted<sup>[23]</sup>. In the above studies, improvements in lipid profiles as well as glucose tolerance status have been observed with orlistat in comparison to placebo<sup>[23]</sup>.

Bachmann *et al* showed that insulin sensitivity was improved significantly after three months of orlistat (120 mg t.i.d, n=6) administration by 42% (p<0.05)<sup>[24]</sup>. This effect was independent of changes in body weight. In more recent study using larger population (n=369), Nicholls showed in two years study that orlistat improved glycaemic control and reduces dependence on antidiabetic therapy<sup>[7]</sup>. "Orlistat manufacturers Roche Pharmaceutical Company are hopeful that these results will strengthen their application to regulatory authorities in the US, Canada and the EU for type 2 diabetes" Nichollos said<sup>[7]</sup>. In a six months of orlistat treatment, both total cholesterol and low-density lipoprotein (LDL) cholesterol are reduced significantly in comparison to placebo (p<0.001)<sup>[25]</sup>. However, concentration of high-density lipoprotein (HDL) was also decrease to a similar extent.

**Indications and contraindications:** Orlistat has been approved by FAD for up to 2 years use in the treatment of obesity (BMI  $\geq 30$  kg/m<sup>2</sup>) or obesity associated with risk factors (BMI  $\geq 28$  kg/m<sup>2</sup>) in white populations<sup>[8]</sup>. The manufactures recommend that the treatment should be initiated only if at least 2.5 kg loss has been achieved during the first four weeks depending on diet alone; and the drug should be discontinued after twelve weeks if

weight loss is not 5% of original body weight<sup>[26]</sup>. Modification of diet is an important factor in the drug response so that meals should be balanced and rich in fibers and has low caloric. Orlistat has been shown to give some improvement on diastolic blood pressure in comparison to baseline (which measured after four weeks of diet control rather than the blood pressure at entry)<sup>[27]</sup>. Hsieh *et al*<sup>[18]</sup> reported that orlistat can decrease and increase the adipose-tissue secretory proteins leptin and adiponectin, respectively<sup>[18]</sup>. The optimum dose for orlistat as antiobesity is 120 t.i.d at or within one hour of meals. The drug is available in 30, 60, and 120 mg pills.

Orlistat is not recommended for children under ten years and pregnant women or at maternity period<sup>[28]</sup>. It also contraindicated in chronic malabsorption syndrome or cholestasis (see below)<sup>[28]</sup>. As all other medication the patient must not have sensitivity to orlistat or any of its excipients. Up to February 2005, no report has been found on orlistat overdose or toxicity. The drug should be taken under medical supervision for optimal results

**Adverse effects:** No serious adverse effects have been reported during orlistat therapy. Recently, in a short-term study, Kaya *et al*<sup>[21]</sup> revealed that orlistat has several mild gastrointestinal adverse effects<sup>[21]</sup>. The adverse effects include diarrhoea, flatulence, oily spotting and faecal incontinence.

Finer *et al*<sup>[29]</sup> showed similar effects but in higher incidence rate (58% of patients). In contrast to above studies, other clinical studies reported less frequent adverse effects. Aronne<sup>[23]</sup> stated that these adverse effects are transient and mild with over 50% of episodes <1 week in duration and most of them is in the first year of treatment (80%). Orlistat had no effect on gastric or pancreatic secretion, and gastric emptying time. Hopman *et al*<sup>[30]</sup> suggested that orlistat may increase the possibility of gallstones formation due to the decrease of meal-related contraction of gallbladder.

**Drug interactions:** Orlistat has no drug-drug interaction with most of drugs either having narrow therapeutic window or taken specifically by obese such as antihypertension, antidiabetics and cardiotoxic medications. A single dose of the compound showed no interaction with atenolol, captopril, digoxin, glyburide, lasix, nifedipine, oral contraceptive, phenytoin, furosemide and warfarin (reviewed in by Harp references 28 and 31). Orlistat increases paravastatin concentration by up to 33%, which result in increase of its antilipidaemic properties but not in half-life<sup>[31]</sup>. No interaction between orlistat and alcohol has been reported yet. In contrast to above substances, the concentration of cyclosporine decrease when co-administered with orlistat to subtherapeutic levels<sup>[32,33]</sup>. Colman *et al*<sup>[31]</sup> and Nagelel *et al*<sup>[32]</sup> thought this decrease in plasma concentration is

due to the decrease in absorption rather than a genuine enzymatic interaction. Thus it is recommended that orlistat not be coadministered with this immunosuppressant.

Several reports indicated that no interaction between either lipid soluble vitamins or  $\beta$ -carotene and orlistat, this is in part because the drug inhibits only 30% of fat absorption i.e. 70% of fat with vitamins supplement is absorbed<sup>[28,34,35]</sup>. Similarly, orlistat had negligible or no effect on serum hormones such as insulin, thyroxine and catecholamines<sup>[36]</sup>.

**Conclusion:** Orlistat is a novel antiobesity agent, which selectively and potently inhibits the absorption and hydrolysis of fat that result in 30% decrease in fat absorption. It had withdrawn the attention of media and researcher during the last three years due to its pharmacoeconomic merit. From the literature, orlistat seems to be safe and promising drug. Its adverse effect and drug-drug interactions seem to be affordable. No reports on overdose and only one case-report were found on the abuse of orlistat with abnormal subject. This drug-report will help in evaluation of orlistat in Saudi Arabia and other country that obesity represents a real challenge in term of quality of life and budget design.

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