Toxicity and Safety Concerns in Orlistat Therapy for Obesity: A Critical Evaluation

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ABSTRACT :
Orlistat is a selective inhibitor of gastric and pancreatic lipase indicated for the treatment of obesity. It is also known to significantly reduce risk of associated co-morbidities such as heart attack, type-2 diabetes mellitus, hypertension and stroke. Recent reports have raised concerns on the possible occurence of serious adverse effects with prolonged use. Orlistat has been shown to inhibit carboxylesterase-2, a major detoxification enzyme, predisposing to severe liver, pancreatic and kidney damage. Orlistat alters the pharmacodynamic response of some drugs when co-administered leading to severe toxicity and reduced efficacy. Safety is a major concern considering the widespread use of this drug both as a prescription and over-the-counter medication. There is need for large-scale observation studies on orlistat use to generate appropriate data that will guide the regulatory agencies in taking relevant decision on continued use of orlistat as anti-obesity drug.
Keywords: Carboxylesterase-2, evaluation, obesity, organ damage, orlistat, safety, toxicity.

INTRODUCTION:

The risk of chronic disease conditions including type-2 diabetes, dyslipidemia, stroke, heart failure, hypertension, fatty liver disease, gallstone are increased with obesity[1]. Orlistat otherwise known as tetrahydrolipstatin, is a saturated derivative of lipstatins. It is a gastrointestinal lipase inhibitor isolated from *Streptomyces toxytricini* approved for treatment of obesity. It should be noted that orlistat therapy does not only confer beneficial effect in weight reduction but reduces the incidence of new cases of diabetes mellitus by 37%[2].

Improvement in cardiometabolic parameters with use of orlistat such as blood pressure, waist circumference and lipid profile can be reasonably attributed to outcome of beneficial weight control[3]. It has been shown that pharmacotherapy of obesity with orlistat was associated with a significant decline in total cholesterol level following adjustment for weight loss in a meta-analysis involving 15 studies[4].

However, the use of orlistat has been linked to permanent liver, kidney and other organ diseases. This may be attributed to interference by orlistat the function of carboxylestrase-2, which plays an important role in detoxification of the liver, kidneys and gastrointestinal tract[5].

This study critically reviewed the effects of orlistat therapy on weight and glycemic control highlighting its impact on organic toxicity particularly the liver and kidneys with a view to ensuring safety in its use as a prescription and over-the-counter medication.

THERAPEUTIC BENEFITS OF ORLISTAT USE

Orlistat therapy is useful in modest reduction in weight loss particularly when the impact of lifestyle modification is inadequate in the treatment of obesity. It received approval from United States Food and

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Drug Administration (FDA) and European Medicines Agency (EMA) for long term treatment of obesity, which is a chronic condition. Gastric and pancreatic lipases are inhibited by orlistat reducing absorption of fat in the intestines, thereby encouraging weight loss. This is associated with malabsorption of fat soluble vitamins (ADEK) necessitating use of vitamin supplements. A systematic review concluded that addition of orlistat to dietary intervention significantly improved weight loss[6]. Another systematic review and meta-analysis reported that patients on orlistat lost significantly more weight than those taking placebo[7]. It has been shown that improvement in both weight loss and maintenance can be achieved by combining orlistat therapy with lifestyle and behavioural interventions[8]. A study has revealed that though the toxicity of orlistat may be unpleasant and deter users; it may also help to educate and encourage them towards more focused behavioural approach to weight control[9]. A study which evaluated predictors of weight loss following orlistat administration revealed that 75% of patients reported both weight loss and reduction in BMI at the end of six months[10]. The study further revealed that the beliefs and behavioural changes occurring in the course of orlistat therapy are better predictors of outcome than the baseline variables.

The weight-independent improvement in glycemic control to orlistat therapy may be attributed to a decrease in post-prandial NEFA (non-esterified fatty acid) concentration. A multicentre randomized double blind placebo controlled study reported clinically significant improvement in glycemic control and lipid profile in type-2 diabetic patients who were obese[11]. Retrospective analysis of pooled data from multicentre double blind placebo-controlled studies reported improvement of glycemic control with orlistat independent of weight loss[12]. The increased plasma levels of NEFA in obesity is associated with incidence of insulin resistance in type-2 diabetes[13]. Hence, the sustained decrease of NEFA concentration in obese individuals with diabetes mellitus or impaired glucose tolerance has been shown to improve sensitivity of glucose metabolism and oral glucose tolerance to insulin[14].There is decrease in visceral adipose tissue more than other adipose stores consequent on reduction in dietary fat absorption with orlistat treatment. The above observation has been validated by several studies which revealed that orlistat therapy significantly reduced waist circumference in subjects with type-2 diabetes relative to contro[l5-16].

Hence, the significant reduction in waist circumference attributed to orlistat therapy may be associated with a decrease in visceral adipose tissue[17]. Orlistat treatment has been shown to increase post-prandial plasma glucagon-like peptide (GLP-1) concentration[18].

The inadequate survival of pancreatic beta cells and development of insulin resistance can be linked to visceral adipose tissue[19]. A dose dependent increase in plasma GLP-1 has been demonstrated following ileal infusion of lipid in volunteer subjects[20].The increased secretion of glucose-dependent insulinotropic peptide and glucagon-like peptide 1(GLP-1) may be attributed to increase in intestinal gut content due to decreased absorption of fat, stimulating insulin secretion[21]. Hence, orlistat treatment blunts the postprandial rise in glucose and enhances insulin secretory response following meals in obese diabetic patients. The increase in prevalence of type-2 diabetes has been linked to intra-abdominal visceral adiposity as major modifiable risk factor[22].

There is minimal absorption of orlistat in the gastrointestinal tract, therefore, no noticeable systemic effect[23]. However, orlistat is eliminated alongside the non-absorbed unsplit triglyceride, while ingested fat absorption is reduced to approximately 33%[24].

A study reported significant improvement in the lipid profile and anthropometric risk factors and diabetic metabolic status of obese diabetic patients treated with orlistat plus diet relative to the control treated with placebo plus diet[16].

TOXICITY PROFILE

The link between acute kidney injury and orlistat therapy has been demonstrated[25]. Incidence of nephrotoxicity manifesting as acute oxalate nephropathy associated with orlistat use has been reported[26]. The incidence of renal stone formation is increased with orlistat use. The underlying mechanism of acute kidney injury associated with orlistat use is related to enteric hypoxaluria, resulting from unabsorbed fat in the small intestine, leading to formation of calcium soaps with consequent reduction in free enteric calcium[27]. The resultant increase in intestinal oxalate absorption and renal excretion leads to supersaturation and precipitation of calcium oxalate crystals in the renal tubules predisposing to the risk of acute kidney injury (AKI). It should be noted that the establishment of causality between drug exposure and adverse event remains challenging despite connection between orlistat and AKI[28].

A study concluded that sufficient evidence exists to attribute orlistat use to acute kidney injury[29]. It however, maintained that it was difficult to unequivocally confirm causality in the background of adverse drug event, in the absence of substantive evidence from multiple observational studies or randomized trials.

Alarm about a possible connection between orlistat therapy and acute liver injury was first raised by the United States Food and Drug Administration (FDA) [30]. The FDA received reports of liver problems asso-

ciated with orlistat use. A study reported severe liver injury following orlistat treatment attributed to inhibition of a major detoxification enzyme in the liver known as carboxylesterase, manifesting as elevated hepatic serum enzymes, hepatic failure, progression to death or need for liver transplantation. Hypersensitivity is postulated as a possible mechanism of liver damage consequent on orlistat therapy, though feature of hypersensitivity is not prominent and no autoimmune markers were found. Incidentally, no substantive evidence was found linking orlistat with hepatic dysfunction in a meta-analysis of clinical trial data[31]. The possibility of severe hepatotoxicity with orlistat treatment is not backed by evidence from preclinical studies. Evidence of mild hepatic dysfunction exhibiting non-statistically significant increase in the liver enzyme, alanine aminotransferase and bilirubin following orlistat therapy compared with placebo was revealed in a meta-analysis of some clinical trials.

A study conclusively revealed that incidence of acute hepatotoxicity was significantly raised in the period both immediately before and after commencement of orlistat therapy, suggesting that the higher risks of liver damage associated with commencement of therapy may reflect changes in health condition associated with decision to commence rather than causal effect of orlistat treatment[32].

Gastrointestinal adverse effects include frequent bowel movements, faecal incontinence and steatorrhoea which are minimized by adhering to reduced calorie low fat diet. Persistent compliance with low-fat diet may be associated with decrease in gastrointestinal related adverse effects which may be severe at onset but decrease with time. A study reported potential risks of iatrogenic orlistat-induced pancreatic insufficiency and steatorrhoea linked to bone disease, associated with long term steatorrhoea and chronic pancreatitis[33].

CONCLUSION

In conclusion, there is no doubt that orlistat therapy has beneficial effects in weight loss and glycemic control. This, however, may be constrained by organ toxicity involving particularly the kidneys, liver and gastrointestinal tract. The outcome of human genome project has provided novel tools for validation of gene expression changes as predictive biomarkers of toxicity. Consequently, it is possible to identify individuals at risk of toxicity with orlistat use, with a view to individualizing therapy based on genetic profile. Hence, the need for futher large scale observational studies on orlistat use to generate appropriate data that will guide regulatory agencies in taking relevant decision on continued use of orlistat as anti-obesity agent is advocated.

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