Obesity management: Update on orlistat

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Abstract: Over the past 20 years obesity has become a worldwide concern of frightening proportion. The World Health Organization estimates that there are over 400 million obese and over 1.6 billion overweight adults, a figure which is projected to almost double by 2015. This is not a disease restricted to adults – at least 20 million children under the age of 5 years were overweight in 2005 (WHO 2006). Overweight and obesity lead to serious health consequences including coronary artery disease, stroke, type-2 diabetes, heart failure, dyslipidemia, hypertension, reproductive and gastrointestinal cancers, gallstones, fatty liver disease, osteoarthritis and sleep apnea (Padwal et al 2003).

Modest weight loss in the obese of between 5% and 10% of bodyweight is associated with improvements in cardiovascular risk profiles and reduced incidence of type 2 diabetes (Goldstein 1992; Avenell et al 2004; Padwal and Majumdar 2007). Orlistat, a gastric and pancreatic lipase inhibitor that reduces dietary fat absorption by approximately 30%, has been approved for use for around ten years (Zhi et al 1994; Hauptman 2000). There is now a growing body of evidence to suggest that Orlistat assists weight loss and that it may also have additional benefits. The aim of this review is to provide a brief update on the current literature studying the efficacy, safety and significance of the use of Orlistat in clinical practice.

Keywords: obese, weight, diet, orlistat, hypertension, cholesterol

Introduction

Over the past 20 years obesity has become a worldwide concern of frightening proportion. The World Health Organization estimates that there are over 400 million obese and over 1.6 billion overweight adults, a figure which is projected to almost double by 2015. This is not a disease restricted to adults – at least 20 million children under the age of 5 years were overweight in 2005 (WHO 2006). Overweight and obesity lead to serious health consequences including coronary artery disease, stroke, type-2 diabetes, heart failure, dyslipidemia, hypertension, reproductive and gastrointestinal cancers, gallstones, fatty liver disease, osteoarthritis and sleep apnea (Padwal et al 2003).

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Methods

Search strategy

Randomized controlled trials, reviews and meta-analyses of Orlistat were included in an electronic search of MEDLINE (1966–2007) and the Cochrane Register of

Controlled Trials (1998–2007). The trials were not limited by language of publication. Bibliographies of all identified randomized trials and review articles were reviewed for additional studies of interest. Two investigators (BD and AD) reviewed all citations retrieved to identify potentially relevant information for this review.

Results

Weight loss in adults

Orlistat is associated with a small but significant weight loss of around 3% more than diet alone in overweight and obese people (BMI ≥ 27). A recent Cochrane meta-analysis including eleven randomized controlled trials using 120 mg Orlistat three times a day found 2.7 kg (95% CI: 2.3 to 3.1) or 2.9% (95% CI: 2.3 to 3.4) greater weight loss in the Orlistat group when compared to placebo. Pooled results showed a larger number of participants in the Orlistat group achieved clinically significant weight loss, with 21% (95% CI: 19–24) and 12% (95% CI: 8 to 16) achieving ≥5% and ≥10% weight loss respectively. There were also greater reductions in waist circumference with Orlistat therapy compared to placebo with reductions from 0.7 to 3.4 cm ($P < 0.05$) (Padwal et al 2003).

The common finding that some patients achieve dramatically better weight loss results with Orlistat than others has important economic implications. One analysis, involving overweight and obese non-diabetics, suggests that Orlistat is cost effective only if those achieving at least 5% weight loss after 3 months continue with therapy (Lacey et al 2005).

Maintenance and attrition rates

An important aspect of any weight management strategy is the prevention of weight regain after initial weight loss. Although there is no data on long-term weight loss, medium term studies show that weight loss is generally maintained in patients who continue Orlistat therapy. A four year double-blind, randomized, placebo-controlled trial with Orlistat including 3304 overweight patients (XENDOS study) showed mean weight loss after 4 years was significantly greater with Orlistat (5.8 kg vs 3.0 kg with placebo; $P < 0.001$) (Torgerson et al 2004). Furthermore, the 2003 Cochrane meta-analysis showed that Orlistat-treated patients regained a smaller percentage of weight compared to placebo-treated patients ($P < 0.05$ for all studies) over 2 years (Padwal et al 2003).

A recent randomized controlled trial looking specifically at Orlistat 120 mg three times a day as a weight maintenance treatment after weight loss with very low energy diet (VLED) demonstrated significantly reduced weight regain after 3 years (4.6 kg vs 7 kg, $P < 0.02$) (Richelsen et al 2007).

Taking into account high attrition rates, medium term weight maintenance on Orlistat therapy is markedly reduced. The Cochrane 2003 meta-analysis found high attrition rates ranging from 14% to 52% (average 33%) during the weight loss phase of Orlistat trials. In the XENDOS study, intention to treat analysis which took into account the 48% attrition rate showed a smaller yet significant weight loss with Orlistat (3.6 kg vs 1.4 kg with placebo; $P < 0.001$) over 4 years (Torgerson et al 2004).

Pharmacoepidemiological studies seem to indicate that attrition rates in clinical practice are even higher (64%–77%) and the major causes of cessation of treatment are high cost and side effects (Vray et al 2005).

Adolescents

While most literature involves adults, a few studies have now assessed the impact of Orlistat induced weight loss on adolescents. One 54 week multi-centre trial comparing Orlistat (N = 357) to placebo (N = 182) in obese 12 to 16 year olds showed that BMI decreased in both groups at 12 weeks and then stabilized in those receiving Orlistat, while increasing in the placebo-treated group. At study end, BMI had decreased by 0.55 kg/m^2 in those treated with Orlistat and increased by 0.31 kg/m^2 in those in the placebo group ($P = 0.001$). Waist circumference decreased in the Orlistat group but increased in the placebo group ($P < 0.05$) (Chanoine et al 2005). However, in a 6-month randomized, double-blind, placebo-controlled trial involving forty adolescents between 14 and 18, Orlistat did not significantly reduce BMI at 6 months (Maahs et al 2006).

Comorbidities

As previously discussed, a weight loss of 5 to 10 percent can significantly reduce the risk factors for diabetes (Knowler et al 2002) and cardiovascular disease in high risk patients (Douketis et al 2005). Orlistat has been shown to be safe and more effective than diet alone in modifying some of the risk of coronary artery disease (Lindgarde 2000). Independent of weight loss, it is important to look at the effect of Orlistat on obesity-related co morbidities.

Type 2 diabetes mellitus

A 2005 Cochrane meta-analysis involving 22 RCTs examining the benefits of pharmacotherapy for weight loss in type-2 diabetes provides evidence that Orlistat can achieve

modest but statistically significant short term weight loss when used as a primary weight reduction strategy among adults with type 2 diabetes. Pooled data on Orlistat over all follow-up periods demonstrated a loss of 2.0kg (95% CI: 1.3 to 2.8). Pooled reduction for HbA1c was 0.5% (95% CI: 0.3 to 0.6) with follow-up between 24 and 57 weeks (Norris et al 2005).

Over four years of treatment with Orlistat in the XENDOS study, the risk of developing diabetes was found to be 37.3% lower compared to placebo (P = 0.0032) (Torgerson et al 2004). In the 21% of subjects that had impaired glucose tolerance at baseline, the incidence of diabetes over the 4 years was decreased by 45.0% with Orlistat therapy. This finding has been supported by a more recent RCT which showed that the incidence of new type-2 diabetes was significantly decreased in patients using Orlistat for weight maintenance after initial weight loss (8/153 new cases type-2 diabetes vs 17/156 cases, P = 0.041) (Richelsen et al 2007).

Hypertension and dyslipidemia

Several meta-analyses have shown modest improvements in blood pressure and serum cholesterol in patients taking Orlistat.

The 2003 Cochrane meta-analysis showed a significant net decrease in systolic blood pressure in the Orlistat group of 1.8 mmHg (95% CI: 0.9 to 2.6), and diastolic BP 1.6 mmHg (95% CI: 0.7 to 2.4). There were also greater reductions in total cholesterol levels 0.33 mmol/L (95% CI: 0.28 mmol/L to 0.38 mmol/L) and LDL 0.27 mmol/L (95% CI: 0.22 to 0.31). No clinically significant effects on triglycerides or HDL cholesterol were observed (Padwal et al 2003). These changes seem to represent an effect of Orlistat on lipid malabsorption rather than an effect of weight loss alone (Dixon and O'Brien 2001, 2002; Mittendorfer et al 2001).

A more recent review of 28 RCTs comparing Orlistat to placebo for 6 months supported this data, showing a significant decrease in total cholesterol 0.3 mmol/L (0.57 to 0.28) and LDL 0.34 mmol/L (0.36 to 0.32) both P values <0.001. Smaller decreases were seen in serum triglycerides 0.08 mmol/L (0.1 to 0.06, $P < 0.001$) and HDL 0.06 (0.011 to 0.01), p = 0.02 (Hutton and Fergusson 2004).

The 2005 Cochrane meta-analysis involving type 2 diabetics also showed that Orlistat was associated with statistically significant improvements in total cholesterol, LDL, and triglycerides that were sustained at 52 weeks follow up (Norris et al 2005).

Other

Other obesity-related co morbidities which have been studied include non alcoholic fatty liver disease and disorders of menstrual cycle. A recent RCT involving 44 patients with NAFLD showed that Orlistat improves serum ALT levels and steatosis on ultrasound in NAFLD patients. The authors argue that this effect is beyond that expected from the weight reduction alone (Zelber-Sagi et al 2006). There is limited evidence to suggest that Orlistat may be effective in the treatment of women with obesity and menstrual cycle disorders (Totoian et al 2006).

Adverse effects

As a result of its mode of action, the predominant adverse effects of Orlistat occur directly or indirectly via the gastrointestinal tract. The bioavailability of Orlistat is less than 1% (due to low systemic absorption and high first-pass metabolism) (McNeely and Benfield 1998), and thus direct systemic side effects are less common than with other anti-obesity medications.

The most commonly reported adverse effects of Orlistat include steatorrhoea, bloating, oily spotting, fecal urgency and fecal incontinence. The percentage of patients experiencing at least one of these side effects appears to be around 16% to 40% (Padwal et al 2003). Perhaps the most psychologically disturbing side effect, fecal incontinence is found in around 7% of patients. There is some concern that Orlistat may lower the absorption of the fat soluble vitamins A, D, E and K (McNeely and Benfield 1998; Sjostrom et al 1998; McDuffie et al 2002). A RCT investigating the impact of Orlistat on vitamin D absorption, bone turnover and bone density found that Orlistat induces a relative increase in bone turnover and a net resorption of bone, possibly due to malabsorption of vitamin D and calcium (Gotfredsen et al 2001). However, the authors argue that these changes can be explained by weight loss itself. The XENDOS study showed reductions in all fat soluble vitamins except vitamin D. Significant numbers of patients using Orlistat over a prolonged period will need multivitamin supplements containing fat-soluble vitamins (Sjostrom et al 1998; Finer et al 2000). Patients should be advised to take them at least 2 hours before or after the administration of Orlistat (Orlistat: 2007).

There is some concern that Orlistat may be associated with increased risk of colon cancer. Recent preliminary research on rats shows an association with Orlistat and increases in colonic preneoplastic markers (Garcia et al 2006). Further research in humans is required. The increased

presentation for free fatty acids to the lower gastrointestinal tract, produced by combining a lipase inhibitor with a fatty diet, is thought to increase oxalate absorption and thus heighten risk of kidney stones and renal impairment (Ferraz et al 2004; Singh et al 2007).

Drug interactions

As vitamin K absorption may be decreased, warfarin anticoagulation may be potentiated during Orlistat therapy (MacWalter et al 2003). Therefore, patients stabilised on warfarin who commence Orlistat should be monitored for changes in INR. Other potential drug interactions include a reduction in the absorption of amiodarone (Zhi et al 2003) and cyclosporine (Zhi et al 2002).

Conclusion

There are consistent data showing that Orlistat provides a modest yet significant amount of weight loss of around 3% more than diet alone in overweight and obese adults. This weight loss appears to be maintained in the medium term in patients who continue therapy. As with any therapy, some patients tend to achieve better results than others. While weight loss of greater than 5% is generally considered clinically significant and may guide patient selection for long-term treatment, the benefit of lower levels of weight loss in those with comorbidities should not be underestimated.

Importantly, Orlistat has been shown to improve glycaemic control in type-2 diabetes and reduce the risk of developing diabetes in overweight and obese individuals with impaired glucose tolerance. It has also been linked to small improvements in blood pressure and lower cholesterol measurements than expected for the level of weight loss. Initial evidence also indicates that Orlistat may be useful in the management of NAFLD, menstrual dysfunction and overweight and obesity in adolescents.

An important distinction however, is whether the relatively small effects of Orlistat on predictors of cardiovascular risk, such as HbA1c, blood pressure and cholesterol, are useful surrogate end points as there is no data on cardiovascular morbidity or mortality. High attrition rates call into question the tolerability, efficacy and cost of Orlistat in clinical practice, as does the lack of long-term safety data.

Given the lack of efficacious non-surgical treatments for overweight and obesity, Orlistat does have a place in current clinical practice. Where modest weight loss will benefit those with obesity comorbidity, the addition of Orlistat to a program of lifestyle change, diet and physical activity, should be considered.

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