EDITORIAL

Orlistat (Xenical) in the Management of Obesity

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The term "obesity" implies an excess of adipose tissue (fat) and excess adiposity is a health risk.[1,2] In most cases it develops in the absence of any underlying disease process. It is always due to greater calorie intake than is expended; the mystery lies in the cause of the energy imbalance.[2] Recently there has been a tremendous surge of interest in understanding the mechanisms controlling energy homeostasis following the identification of the ob gene and its protein product (termed "leptin" from the Greek work "leptos", meaning thin) by Zhang et al in 1994.[3]

The most widely used measurement in clinical practice is the Body Mass Index (BMI); defined as the ratio of the body weight (in kilograms) divided by the square of the height (in metres). Traditionally in the adult, the normal range of the BMI is 20 to 25; a BMI of 25.1 to 29.9 is overweight and a BMI of 30 and above is obese. Recently,[4] for the Asia Pacific region, the recommended normal BMI is 18.5 to 22.5; a BMI of $\geq$23 is overweight. A BMI of 23 to 24.9 is regarded as At Risk; 25 to 29.9 is Obese I and $\geq$30 is Obese II.[4]

As society becomes more developed and affluent, the prevalence of obesity increases. In Singapore, a national health survey (1998)[5] of the adult population showed that 6% of Singaporeans are obese (Body Mass Index or BMI $\geq$30) and 24.4% are overweight (25 < BMI < 30) or pre-obese. A higher proportion of men (28.6%) are overweight compared with women (20.3%) whereas more women (6.7%) than men (5.3%) are obese. Obesity is most prevalent in Malays (16.2%), followed by Indians (12.2%) and Chinese (3.8%). The highest proportion of obesity is noted in the 50 to 59 years age groups.[5] In contrast, in the USA 20% to 30% of adult men and 30% to 40% of adult women are obese.[1]

Obesity is a health risk and even mild obesity increases the risk of premature death, diabetes mellitus, metabolic syndrome, hypertension, hyperlipidaemia, atherosclerosis, coronary artery disease, gout, gall bladder disease, respiratory disease, arthritis and certain types of cancer.[1,4] A further reason to treat obesity is that it is often not a desirable aesthetic, social and cultural trait.

A team approach is required for the successful management of obesity. The physician/endocrinologist requires the help of the dietician, behavioural therapist/psychiatrist, exercise therapist, surgeon, etc. Managing an obese patient often requires the full cooperation of the family and often it involves managing the whole family as well.

An underlying cause of the obesity has to be carefully excluded; although secondary obesity is rare, the differential diagnosis is very long.

Caloric restriction is the cornerstone of weight reduction. If energy intake is less than energy expenditure, weight loss will occur. Any adult truly eating 1000 calories or less daily will lose weight.

After an adequate period (about 3 months) of caloric restriction, exercise and behavioural therapy (where available) fail to achieve desirable weight loss, an anti-obesity drug is indicated. The role of anti-obesity agents has been reviewed recently.[6] The first anti-obesity drug used to treat obesity was amphetamine (adrenergic agent); its use was abandoned due to its addictive tendency.

Adrenergic agents suppress the appetite; various preparations of phentermine and Mazinol are available; as they have stimulant action on the central nervous system, only short-term use is recommended.[4] Serotonergic drugs such as fenfluramine (Ponderax) and dexfenfluramine (Adifax) were widely used until they were withdrawn in 1997 because of their side effects (valvular heart disease and pulmonary hypertension).[6]

Fluoxetine (Prozac) is an inhibitor of serotonin uptake and is marketed as an antidepressant; it also produces weight loss.

The intestinal lipase inhibitor, Orlistat (Xenical) is a new class of non-systematically-acting drug for the treatment of obesity. It was launched by Roche in Singapore in 1999. It is a potent, specific and long-acting inhibitor of gastric and

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pancreatic lipases; it inhibits the absorption of ingested fat by 30%. Xenical has been reported to be effective in the long-term treatment of obesity (up to 2 years or longer); besides weight loss it is reported to reduce total and LDL-cholesterol, reduces hypertension and improves glycaemic control in diabetes.[7-9]

In the European Multicentre Orlistat Study Groups (1998),[9] from the start to the end of Year 1, the Orlistat group lost more weight than the placebo group (10.3 kg vs 6.1 kg). During Year 2, patients who continued with Orlistat regained on average half vs much weight as those patients who switched to placebo.[9] Zavoral (1998)[10] reported that in 3132 obese patients treated with Orlistat or placebo pooled from 5 randomised, double-blind, placebo-controlled trials in conjunction with a hypocaloric diet, Orlistat produced significantly more weight loss (9.2% vs 5.8%, $P < 0.001$) compared to placebo. Further Orlistat-treated patients had significantly greater improvements than placebo-treated patients in total cholesterol, low-density lipoprotein-cholesterol, triglycerides and apolipoprotein B.[10] In addition, Orlistat had a beneficial effect on oral glucose tolerance tests, waist circumference and systolic and diastolic blood pressure.[10] Orlistat was well tolerated and had a similar safety profile to placebo.[10]

Side effects of Orlistat are largely gastrointestinal and related to the pharmacological effect of the drug on preventing the absorption of ingested fat; these include oily spotting from the rectum, flatus with oily discharge, faecal urgency, oily stools etc. The incidence of adverse events decreased with prolonged use of the drug.

The most troublesome side effect of Xenical is social-aesthetic: leakage of oily material, sometimes without warning but usually with the passage of flatus. Patient should be told of this side effect and it is wise to increase the dosage gradually. The side effects can be minimised with slightly reduced food (and especially oily food) consumption.

Contraindications to Orlistat include malabsorption, cholestasis, breast feeding and hypersensitivity to the drug. It is not recommended for use in pregnancy and in children.

Currently Orlistat is the only anti-obesity drug available for relatively long-term management of obesity. It is especially useful in treating the obese non-insulin dependent diabetic, who is often hypertensive and hyperlipidemic.[11] In such a patient, Orlistat will help reduce the weight, blood pressure, lipids and blood glucose.

Treatment of obesity is slow and difficult; Orlistat (Xenical) is a useful anti-obesity drug and its use is rapidly increasing. It facilitates weight reduction and helps to maintain it.

The best treatment of obesity remains prevention.

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