UNIT NO. 6

PHARMACOTHERAPY AND SURGERY FOR OBESITY

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ABSTRACT

The Ministry of Health Clinical Practice Guidelines (April 2004) for obesity recommends that drug therapy should be considered when BMI exceeds 27.5 kg/m² in an Asian population such as ours. The two most commonly targeted area of action for anti-obesity drugs are the suppression of appetite by centrally active medication that alter monoamine neurotransmitters and reducing the absorption of fats from the gastrointestinal tract. Currently, there are two anti-obesity medications approved by FDA i.e. Sibutramine (Reductil®) and Orlistat (Xenical®). It is likely that anti-obesity medications used as an adjunct to management need to be continued for long periods. Bariatric surgery should be considered for patients with morbid obesity (BMI>40 kg/m²) or those with severe obesity (BMI>35 kg/m²) but with serious medical problems.

INTRODUCTION

Therapies that claim to induce weight loss abound in the media and consumers are constantly looking for that magic pill that will allow them to eat and yet not put on weight. The truth of the matter is that such therapies are not available and caloric restrictions are key pillars in the management of obesity. Therefore, in the subsequent sections discussing pharmacotherapy and surgery, unless otherwise mentioned, caloric restrictions must be concurrently implemented.

How can we assess the true efficacy of any therapy, be it pharmacotherapy or surgery? Increasing body mass index (BMI) or weight has been shown in epidemiological data to be associated with increased mortality[1-3], the majority of which are from cardiovascular complications. Therefore, obesity should no longer be considered only as a cosmetic or image problem because we have good evidence that it is associated with a number of medical problems and consequences. Obesity can be considered as a risk factor for the development of diseases such as coronary heart disease, hypertension and diabetes mellitus (DM) as well as being a complex syndrome where several risk factors co-exist. Furthermore, diseases associated with obesity are not simply related to amount of fat in the body but more significantly with the distribution of the fat. Abdominal or visceral fat is more likely to be associated with complications of obesity.

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PHARMACOTHERAPY (PRESCRIBED MEDICATION)

1. When do we start anti-obesity drugs?

The Ministry of Health Clinical Practice Guidelines (April 2004) for obesity recommends that drug therapy should be considered when BMI exceeds 27.5 kg/m² in an Asian population such as ours. When co-morbidities of obesity, such as DM, hyperlipidaemia, coronary artery disease (CAD) and obstructive sleep apnoea (OSA) are present, therapy can be initiated even when BMI is between 25 to 27.4 kg/m². However, it is reasonable to adopt the principle that pharmacotherapy should be used as an adjunct to the long term management of obesity rather than the primary therapy. Many physicians have reservations about the use of anti-obesity drugs and rightly so because of past experience. Problems arising from the use of amphetamine-derived addictive stimulant medication and the use of fen-phen medication with its associated cardiac complications are good reminders that the use of anti-obesity drugs should be used only when indicated.

2. Targets of action

The two most commonly targeted area of action for anti-obesity drugs are the suppression of appetite by centrally active medication that alter monoamine neurotransmitters and reducing the absorption of fats from the gastrointestinal tract. Whether the medication acts centrally to suppress appetite or peripherally to block the absorption of fats, patients must deliberately change or alter their behaviour before weight loss can occur. It is important that the pharmacotherapy must translate into behavioural change or the medication will be ineffective. That is why it is important for patients on such medication to understand that the pharmacotherapy should be used as an adjunct and not as substitute for lifestyle change. In my own practice, I find it extremely useful not to initiate medications until patients have been able to demonstrate some weight loss by lifestyle modifications as this will reinforce the message.

3. What is the evidence for benefit?

Currently, there are two anti-obesity medications approved by FDA i.e. Sibutramine (Reductil®) and Orlistat (Xenical®). What is the evidence that these medications are effective for reducing weight? In a systemic review and meta-analysis of good randomised controlled trials, a total of 11 studies with orlistat and 3 studies with sibutramine were analysed[4]. The orlistat showed an average of 2.7 kg weight loss or 2.9% greater weight reduction compared with placebo after one year of treatment. Sibutramine on the other hand showed 4.3 kg weight loss or 4.6% greater weight reduction compared with placebo after a year of treatment. However, there are no

good data on the efficacy of these two anti-obesity agents beyond one year. Although sibutramine is effective in reducing weight, the benefits on obesity related mortality and morbidity has not been proven[5]. Different meta-analysis of the RCT in anti-obesity medications shows minor variations in amount of weight loss. However, no class of drug demonstrated superiority in terms of weight loss and the placebo-subtracted weight loss never exceeded 4 kg[6].

4. Sibutramine (Reductil®)

Sibutramine was approved in the US in 1997. The longest published use of sibutramine comes from the STORM (Sibutramine Trial of Obesity Reduction and Maintenance) Study Group[7]. The weight loss at the end of 2 years was 10.2 kg compared with 4.7 kg in the control group, giving a mean difference in weight of 5.5 kg. The most commonly reported adverse events include headache, dry mouth, insomnia and constipation. It does not appear to adversely affect cardiac valve function. There is need for periodic monitoring of blood pressure and heart rate when medication is initiated. Treatment should start with 10 mg dose and review in one to two months. If there are no side effects but weight has not reduced, then the dose may be increased to 15 mg. If side effects occur, then the medication can be reduced to 5 mg or discontinued if side effects are intolerable. Patients with hypertension can be given sibutramine as long as the blood pressure is well controlled. The drug is contraindicated in patients receiving other centrally acting appetite suppressant agents, Monoamine oxidase inhibitor and anti-depressants such as serotonin, and norepinephrine reuptake inhibitor.

5. Orlistat (Xenical®)

Orlistat was approved in the US in 1999. It is a non-systemic anti-obesity agent that acts on the gastrointestinal tract. Orlistat acts by inhibiting the activity of pancreatic and gastric lipases and thereby reducing the absorption of dietary fat by about 30%. On the average, subjects on Orlistat lose 10% of their weight compared with 6% weight loss in those on placebo[8,9]. In the second year of treatment, those who stayed on the medication regained 1.5 to 3 kg of weight while the placebo group regained 4 to 6 kg in weight. The medication is usually given at 120 mg tid with each fat containing meals or up to one hour after the meal. Adverse effects include increased defecation, flatulence with discharge, oily spotting, faecal urgency or faecal incontinence. It is important to note that subjects taking Orlistat can lose fat soluble vitamins A, D, E, K as well asbeta carotenes and other carotenoids. Therefore, if such vitamin supplements are taken, there should be at least a 2 hour gap before or after Orlistat is taken.

6. When do you stop treatment?

Since obesity is a chronic metabolic disorder that tends to worsen with age, together with other concomitant diseases such as DM, hypertension and hyperlipidaemia, it is likely that anti-obesity medications used as an adjunct to management need to be continued for long periods. There are no data on the long term use of either Sibutramine or Orlistat but it is likely that the medications will be needed to prevent weight regain. While some patients may choose to use their medications intermittently, especially during holidays and periods of indiscretion, most others will need long term medication.

BARIATRIC SURGERY

Bariatric surgery should be considered for patients with morbid obesity (BMI>40 kg/m^2) or those with severe obesity (BMI>35 kg/m^2) but with serious medical problems.

1. What is the evidence of benefit?

Placebo controlled trials of surgery is limited because it is unethical. The US NIH reviewed 5 RCT and showed that surgery resulted in weight loss of between 10 to 159 kg over a one to 5 year period[10]. Similarly, the UK NHS reviewed 6 trials and concluded that gastric bypass resulted in 45 to 65 kg weight loss while gastroplasty resulted in 30 to 45 kg weight-loss. Presently, newer techniques of gastric banding are available. Overall, surgery promoted substantial and prolonged weight loss in patients with extreme obesity[10].

Surgery is generally able to produce a weight loss of approximately 50% of excess weight and that weight loss is maintained in 60% of patients even at 5 years. Therefore it is important to contain expectation and explain to patients that they may not achieve ideal weight even after surgery. However, the substantial weight reduction following surgery will also result in improvement of co-morbid conditions such as Type 2 DM, glucose intolerance, OSA, hypertension, dyslipidaemia and the metabolic syndrome.

2. Types of bariatric surgery

Surgical procedures can be divided into restrictive or malabsorptive types. Restrictive procedures include gastric banding, horizontal and vertical gastroplasty. Malabsorptive procedures include biliopancreatic diversion and jejunoileal bypass. Roux-en-Y gastric bypass combine both restrictive and malabsorptive techniques. Adjustable gastric banding (lap band) has become the most frequently performed laparoscopic bariatric operation in Singapore.

3. Pre-operative evaluation

As many candidates for bariatric surgery have significant co-morbid medical condition, pre-operative evaluation to assess fitness for operation as well as to treat medical conditions is important. A formal psychiatric evaluation is a standard part of the pre-operative evaluation to exclude mental disorders, severe depression, schizophrenia, personality disorders and substance abuse. Patients with these conditions are not suitable candidates for bariatric surgery. The patient also needs to understand the benefits and risk of the procedures and must be prepared for long term follow up, dietary and lifestyle changes.

4. Post-operative follow up

In the immediate post-operative period, patients are given clear fluid on day 1 and then advancing to a pureed diet on day 3 to 4 prior to hospital discharge. Liquid and soft diet should be prescribed for the first month and only progressing to solid food after that. Beverages should be consumed apart from the solid food to facilitate adequate intake of protein calories. The ongoing medical problems need to be managed as well as watching out for complications of operation such as band slippage, incisional hernia, outlet stenosis and pouch dilatation. There must also be surveillance for biochemical abnormalities such as anaemia, calcium deficiency although iron, B12 and folate deficiency are less commonly associated with lap band than with the Roux-en-Y bypass procedure.

OTHER PHARMACOTHERAPY AND OTC PREPARATION

There are a whole host of drugs that have been used for weight reduction. These include:

- Anoretic drugs including noradrenergic (phentermine, mazindol, diethylpropion hydrochloride) & serotonergic (fenfluramine, dexfenfluramine, fluoxetine). Phentermine is the only noradrenergic drug available. The serotonergic drugs have been withdrawn because of adverse effects on heart valves.
- Mazindol is structurally related to tricyclic anti-depressants and acts like an appetite suppressant. However, it was thought to be associated with cardiac events.
- Phentermine is an appetite suppressant and results in 8.1% or 7.9 kg weight loss at 36 to 52 weeks, well tolerated and efficacious[11].
- Ephedrine is a sympathomimetic agent which induces weight loss by increasing thermogenesis. It is often combined with caffeine or caffeine and aspirin in OTC preparation. Good data on benefits are not available as most studies are short term but showed between 1 to 3 kg weight loss compared with placebo.

CHITOSAN (MINUSFAT®)

We had previously studied the use of chitosan for weight reduction in a randomized controlled trial[12]. Chitosan is derived from chitin, a polysaccharide found in the exoskeleton of shellfish such as shrimp, lobster or crabs. Many adverts claim that chitosan causes weight loss by binding fats in the stomach and preventing them from being digested and absorbed and therefore an effective weight reducing agent. A total of 88 normal, obese subjects were recruited, of which 68 completed the study. There was no difference in weight, BMI, lean body mass between those on Chitosan and placebo and female subjects had instead gained weight. The only benefit from Chitosan was an elevated HDL cholesterol.

DIETARY FIBRES (MINULEST®)

Dietary fibres have also been used as weight reducing agents as they could potentially bind fats and also reduce caloric intake because of its bulking properties. A randomized controlled trial using dietary fibre (Minulest®) involving 83 subjects were carried out in Singapore[13]. After 3 months, there was no difference in weight or BMI between active and placebo group. The only demonstrable benefit was a 3.2% reduction in cholesterol and 5.5% reduction in LDL cholesterol.

Other non-prescriptive agents available include:

- Ma Huang and Kola nut supplement (90/192 mg/day ephedrine alkaloids/caffeine). Placebo controlled trial showed 5.3 kg in active treatment vs 3.2 kg weight reduction in placebo group ($p<0.001$).
- Ma Huang and Guarana: 4 kg weight-loss over 8 weeks
- Biolean: 0.73 lb/wk (over 18.7 weeks)
- Phentermine and Satiete: 0.87 lb/wk (over 12.4 weeks)
- Ginseng berry extract: reduces blood glucose and weight in db/db mice

CONCLUSION

In the management of obesity, the attending physician must set realistic goals for the patients. Although aiming for desirable body weight is good, we must realize that often, this is not attainable. Therefore, we must impress upon our patients that even if ideal weight is not attained, losing just 4 to 5kg in weight-loss will translate into significant reduction in cardiovascular risk. We should be aiming for gradual weight loss of not more than 0.5 to 1 kg weight-loss per week. Dietary and lifestyle changes remain key pillars in the management of obesity and pharmacotherapy as well as bariatric surgery should only be used as adjunct to the management. The pharmacological agents are particularly useful in maintaining weight-loss after lifestyle and dietary changes have induced weight changes.

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LEARNING POINTS

- **The Ministry of Health Clinical Practice Guidelines (April 2004) for obesity recommends that drug therapy should be considered when BMI exceeds 27.5 kg/m^2 in an Asian population such as ours.**
- **The two most commonly targeted area of action for anti-obesity drugs are the suppression of appetite by centrally active medication that alter monoamine neurotransmitters and reducing the absorption of fats from the gastrointestinal tract.**
- **Currently, there are two anti-obesity medications approved by FDA i.e. Sibutramine (Reductil®) and Orlistat (Xenical®).**
- **It is likely that anti-obesity medications used as an adjunct to management need to be continued for long periods.**
- **Bariatric surgery should be considered for patients with morbid obesity (BMI>40 kg/m^2) or those with severe obesity (BMI>35 kg/m^2) but with serious medical problems.**