Introduction
Diets and exercise should be the mainstay of management of obesity. Nonetheless, many people put their faith in slimming agents as a quick fix for weight reduction. Their effectiveness appears to be limited as the amount of weight loss is small. The lack of long-term safety data and the occurrence of adverse effects are important consideration. Proprietary slimming products are heterogeneous and may contain drugs that are no longer used because of their toxicity profile. Problems occur because slimming agents are used inappropriately or proprietary products are adulterated with toxic drugs.

Inappropriate Use of Slimming Drugs
In Hong Kong, drugs licensed for the treatment of obesity are orlistat and the appetite suppressants (sibutramine, phentermine, mazindol and amfepramone). These drugs should be used under strict medical supervision. Combination therapy involving more than one anti-obesity drug is contraindicated. We have encountered a number of patients presenting with acute psychosis while taking combinations of appetite suppressants (sibutramine, phentermine and amfepramone). In some instances drugs not intended for use as slimming agents were used for weight reduction (levothyroxine, tiratricol, growth hormone and diuretics). Such “off-label” use is risky to patients and must be discouraged.

Adulteration of Proprietary Slimming Products
Adulterants commonly identified in proprietary slimming products include appetite suppressants (sibutramine, desmethylsibutramine, fenfluramine, N-nitroso-fenfluramine), animal thyroid tissue, laxatives (bisacodyl, phenolphthalein) and drugs to mask the undesirable effects of other adulterants (e.g. propranolol). The adulterants often produce numerous side effects (Table 1). For example, thyroid hormones and thyroid tissues may cause hyperthyroidism and related complications including heart failure and hypokalaemic paralysis. As the quantity of adulterant is poorly standardized, inadvertent overdose can occur. A young woman developed postural syncope after taking a proprietary slimming product adulterated with propranolol.
Most importantly, some adulterants have long been banned because of their toxicity. Fenfluramine is linked to valvular heart disease and pulmonary hypertension. A middle aged woman died of pulmonary hypertension and heart failure after taking a fenfluramine-containing slimming product. N-nitroso-fenfluramine and fenfluramine share a similar structure. They are not registered pharmaceuticals in Hong Kong. Worldwide they caused more than 800 cases of liver toxicity including fatal cases. N-nitroso-fenfluramine induced fulminant liver failure necessitating liver transplantation has been reported locally.

**Adverse Drug Interactions**

Adverse effects can be caused by adverse interactions between slimming product and concurrent medications. For example, anthraquinone and its derivatives are cathartics. They are frequently found in proprietary slimming products. Renal and liver complications resulting from the combined use of non-steroidal anti-inflammatory drugs and anthraquinone-containing slimming agent have been reported in Hong Kong. A young patient developed neurological disorder after taking phentermine together with a slimming product adulterated with sibutramine. Physicians should warn their patients about the risk of drug-drug and drug-herb interactions.

**Conclusion**

Slimming products are popular in Hong Kong. Safety of these products is often overlooked and many unintentional poisonings have occurred. Patients may not disclose the history of using slimming agents. Physicians should be vigilant about the toxic effects and drug-drug interactions involving these agents. They should report suspected cases to the Department of Health for further investigations. Overall speaking, public awareness of the potential problems related to the use of slimming agents is inadequate. Health education on this issue should be enhanced.

**References**


**Table 1. The adverse effects of adulterants in proprietary slimming products**

<table>
<thead>
<tr>
<th>Adulterant</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fenfluramine</td>
<td>Valvular heart disease, pulmonary hypertension</td>
</tr>
<tr>
<td>N-nitroso-fenfluramine</td>
<td>Liver toxicity</td>
</tr>
<tr>
<td>Sibutramine</td>
<td>Increase in blood pressure and heart rate, insomnia, psychosis</td>
</tr>
<tr>
<td>Animal thyroid tissue</td>
<td>Thyrotoxicosis and related complications</td>
</tr>
<tr>
<td>Propranolol</td>
<td>Postural hypotension, bradycardia</td>
</tr>
<tr>
<td>Bisacodyl</td>
<td>Gastrointestinal upset</td>
</tr>
<tr>
<td>Phenolphthalein</td>
<td>Gastrointestinal upset, carcinogenicity</td>
</tr>
</tbody>
</table>

*1Resident Specialist, Toxicology Reference Laboratory, Hospital Authority*
*2Consultant Chemical Pathologist, Toxicology Reference Laboratory, Hospital Authority*
*3Director, Toxicology Reference Laboratory, Hospital Authority*
There are five drugs registered in Hong Kong which are labelled as anti-obesity agents. They belong to three distinct pharmacological classes:

1. Gastrointestinal lipase Inhibitor: orlistat
2. Noradrenergic and serotonergic agent: sibutramine
3. Noradrenergic agents: diethylpropion (also known as amfepramone), phentermine, and mazindol

A summary on the modes of action and range of toxicity of anti-obesity agents are shown in Table 1.

1. Gastrointestinal Lipase Inhibitor

**Orlistat** is a synthetic derivative of lipstatin, a natural lipase inhibitor. Orlistat is minimally absorbed and selectively inhibits gastrointestinal lipases. Accordingly, orlistat cuts down formation of free fatty acids from dietary triglycerides. Additionally, lower luminal free fatty acid concentrations result in malabsorption of cholesterol. Up to 30% reduction in fat absorption occurred with a daily dose of 360mg.

**Adverse Effects:**

Major complaints are mainly gastrointestinal. Soft stools, abdominal pain/colic, flatulence, faecal urgency or incontinence are reported in 80% of patients. However, symptoms tend to improve with continued orlistat use. Orlistat induced malabsorption of fat-soluble vitamins has been reported.

2. Noradrenergic and Serotonergic Agents or Centrally-acting Appetite Suppressants

**Sibutramine** induces weight loss by decreasing appetite via the combined effects on serotonin and noradrenaline reuptake inhibition. Its secondary action in stimulating thermogenesis plays a minor role in weight reduction. The recommended starting dose is 10mg daily, and may be increased to 15mg daily.

**Adverse Effects:**

Dry mouth, anorexia, insomnia, constipation, dizziness and nausea are common side effects of sibutramine. Significant increases in both systolic and diastolic blood pressure and pulse rate have been noted. It should not be used in patients with a history of coronary artery disease, stroke, congestive heart failure or arrhythmias. It should not be used in patients receiving MAO inhibitor therapy.

3. Noradrenergic Agents

a. **Diethylpropion** (also called amfepramone) is an appetite suppressant. Patients with severe hypertension and cardiovascular disease should avoid this drug. Diabetic patients may experience reduced dosage requirements on insulin or oral hypoglycaemics.

b. **Phentermine** acts like amphetamine as appetite suppressant. Phentermine can cause insomnia if taken at night time. Significant rises in blood pressure, palpitations and arrhythmias can occur. Use is not advisable in hypertensive patients and those with unstable cardiovascular function. Phentermine should never be taken by patients on MAO inhibitors or tricyclic antidepressants as it may result in hypertensive crisis. It is also contraindicated in patients with glaucoma since adrenergic stimulation can induce mydriasis.

c. **Mazindol** demonstrates short-term efficacy for weight reduction.
Long-Term Use of Anti-obesity Agents\textsuperscript{2-9}

The issue on the role of medications in weight loss includes:

1. the amount of weight loss is small;
2. the common occurrence of adverse effects; and
3. weight is regained when the anti-obesity drugs are discontinued.

Drugs represent a short-term solution to a long-term problem with only modest benefits. To date, all anti-obesity drug trials have been limited by their high attrition rates and lack of long-term morbidity and mortality data.\textsuperscript{3} If prescribing of such medication is justified, the adverse effect profile of individual drug should be considered. In addition, close monitoring on the occurrence of adverse effects is essential. Until safety data are available, physicians should refrain from prescribing the medications for durations longer than those approved by regulatory authorities. \textit{Of all the drugs discussed above, only orlistat and sibutramine are approved by the US Food & Drug Administration (FDA) and the National Institute for Health and Clinical Excellence (NICE) of UK. The longest published study of orlistat use is 4 years,\textsuperscript{7} and the drug is approved by the FDA for two-year use. For sibutramine, no studies lasting longer than 2 years have been reported, and it is approved by the FDA for one-year use. All other anti-obesity agents should only be prescribed short term (i.e. few weeks).}\textsuperscript{2,4}

Treatment with multiple anti-obesity drugs cannot be recommended. One study showed no greater weight loss with the combination of orlistat and sibutramine than with sibutramine alone.\textsuperscript{8} Pharmacotherapy should be considered a failure and stopped if weight loss is less than 5%, weight is regained, or there is any suspicion of toxicity.\textsuperscript{9}

Summary

Management of obesity must involve lifestyle modification, with a reduction in energy intake and an increase in physical activity. Anti-obesity agents should not be used as first line treatment for obesity. Due to the lack of long-term safety data, these agents are to be employed as short-term measures only, especially with the centrally-acting drugs.

References

<table>
<thead>
<tr>
<th><strong>Anti-obesity agents</strong></th>
<th><strong>Legal classification</strong></th>
<th><strong>Pharmacology or mode of action</strong></th>
<th><strong>Adult daily oral dose or maximum tolerated exposure</strong></th>
<th><strong>Common adverse effects</strong></th>
<th><strong>Symptoms of overdose</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Orlistat*</td>
<td>Prescription Only</td>
<td>Inhibits pancreatic lipase, hence reduce fat absorption</td>
<td>Recommended dose: 120mg tds Max dose: 800mg tds as a single dose or 400mg tds for 15 days or 240mg tds for 6 months</td>
<td>Oily spotting, diarrhea, flatulence, bloating</td>
<td>Oily spotting, flatus with discharge, faecal urgency, increased defecation</td>
</tr>
<tr>
<td>Sibutramine*</td>
<td>Prescription Only</td>
<td>Reuptake inhibitor of both noradrenaline and serotonin receptors to induce satiety</td>
<td>Recommended dose: 10mg-15mg tds</td>
<td>Headache, modest increase in blood pressure and pulse rate and nervousness</td>
<td>Acute overdose of 400 milligrams resulted in a heart rate of 120 BPM</td>
</tr>
<tr>
<td>Diethylpropion (Amfepramone)</td>
<td>Prescription Only Dangerous Drug</td>
<td>Act at adrenergic receptor to induce satiety</td>
<td>Recommended dose: up to 3mg Max dose: Up to 8mg</td>
<td>Intense vasoconstriction, hypertension and tachycardia, associated with hyperactivity and agitation, Cardiac dysrhythmias, cerebrovascular accidents, hyperthermia, coma, and status epilepticus may be seen after overdose</td>
<td></td>
</tr>
<tr>
<td>Phentermine</td>
<td>Prescription Only</td>
<td></td>
<td>Recommended dose: 15mg-45mg Max dose: 90mg</td>
<td>Tachycardia, tremor, shortness of breath, insomnia</td>
<td></td>
</tr>
<tr>
<td>Mazindol</td>
<td>Prescription Only</td>
<td></td>
<td>Recommended dose: up to 3mg Max dose: Up to 8mg</td>
<td>Restlessness, abdominal cramps, hallucination</td>
<td></td>
</tr>
</tbody>
</table>

* Approved by FDA, US and NICE, UK, as adjunct in treatment of obesity.
A 14-year-old girl presented to the Accident & Emergency Department (AED) with palpitations and bad temper after taking a slimming product ordered from the internet for one month. The patient was also noticed by her mother to have pressure of speech and flight of ideas. There was some subjective weight loss but the actual weight reduction was not recorded. The last dose of the slimming product was taken two days before she was seen at the AED. Physical examination showed a blood pressure of 114 / 71mmHg and tachycardia (pulse rate 156 beats per minute). There were no goitre or eye signs suggestive of Graves’ disease. Thyroid function test (TFT) was performed and the results were abnormal (Table 1).

Table 1: Thyroid function test results of Patient 1. The initial TFT results confirmed thyrotoxicosis in this patient. The slimming product was stopped two days before the first presentation. After removal of the exogenous thyroid hormones, the TFT of this patient returned to normal.

<table>
<thead>
<tr>
<th>Time since first presentation at AED</th>
<th>First presentation</th>
<th>10 days</th>
<th>4 weeks</th>
<th>6 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH</td>
<td>0.02</td>
<td>0.03</td>
<td>2.28</td>
<td>2.92</td>
</tr>
<tr>
<td>Free T4</td>
<td>48.1</td>
<td>11.6</td>
<td>10.4</td>
<td>13.1</td>
</tr>
<tr>
<td>Free T3</td>
<td>21.7</td>
<td>4.4</td>
<td>4.2</td>
<td>--</td>
</tr>
</tbody>
</table>

Reference Ranges
- TSH: 0.53 – 3.59 mIU/L
- Free T4: 12.0 – 20.6 pmol/L
- Free T3: 3.5 – 7.7 pmol/L

A 29-year-old lady with a history of depression presented to the AED with a 3-day history of chest discomfort. She was taking a slimming product ordered from the internet for 3 months. Increased agitation and palpitations were noticed shortly after starting this slimming product. There was no obvious change in body weight. Physical examination of this patient showed tachycardia (pulse rate 125 beats per minute) and hand tremors. Blood pressure was 129 / 74mmHg. TFT was checked and the results were abnormal (Table 2). Her thyroid stimulating hormone (TSH) level checked around six months ago was normal.

Table 2: Thyroid function test results of Patient 2. The initial TSH and fT3 results confirmed thyrotoxicosis. The first fT4 level was within the reference range. This might be related to the time of blood sampling since the last dose of the slimming product.

<table>
<thead>
<tr>
<th>Time since first presentation at AED</th>
<th>First presentation</th>
<th>1 week</th>
<th>3 weeks</th>
<th>4 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH</td>
<td>&lt; 0.03</td>
<td>--</td>
<td>&lt; 0.03</td>
<td>0.48</td>
</tr>
<tr>
<td>Free T4</td>
<td>21.0</td>
<td>--</td>
<td>10.4</td>
<td>--</td>
</tr>
<tr>
<td>Free T3</td>
<td>--</td>
<td>15.6</td>
<td>--</td>
<td>2.2</td>
</tr>
</tbody>
</table>

Reference Ranges
- TSH: 0.32 – 5.0 mIU/L
- Free T4: 9.1 – 23.8 pmol/L
- Free T3: 2.2 – 5.4 pmol/L

Both patients were diagnosed to have slimming agent induced thyrotoxicosis. They were advised to stop taking the products and discharged without the need for specific treatment. Follow-up TFT results were also shown in Tables 1 and 2.
Thyrotoxicosis caused by Slimming Product adulterated with Thyroid Tissues (Cont’)

Dr Liz YP Yuen
Ms SW Ng

Case Report

Toxicology Analysis Results

The slimming pills from both patients have the same appearance (Figure 1). Routine toxicology analysis by high performance-liquid chromatography detected sibutramine and caffeine in both samples. The two samples were then analyzed by liquid chromatography coupled to tandem mass spectrometry after enzyme digestion. Thyroid hormones, triiodothyronine (T3) & thyroxine (T4), and related molecules, namely monoiodotyrosine (MIT), diiodotyrosine (DIT), diiodothyronine (T2) and reverse triiodothyronine (rT3) were detected in both. The slimming drugs were stained with hematoxylin and eosin and examined under light microscope. Structures resembling thyroid globules were seen (Figure 2). The latter two analyses confirmed that the slimming products were adulterated with desiccated thyroid tissues.

Discussion

Animal thyroid tissues, sibutramine and caffeine were detected in the two slimming products. Each of the ingredients can cause significant adverse effects. Their use in combination at variable dosages is even more hazardous. The illegal adulteration of weight reducing products with thyroid tissues is known to occur for many years. In Japan, 12 patients developed thyrotoxicosis after taking two weight-reducing herbal medicines known as “Ever Youth” and “Dream Shape”. Both medicines were found to contain thyroid hormones. In France, a slimming drug adulterated with pig thyroid glands caused at least one death and five serious cases of thyrotoxicosis requiring intensive care unit admissions. Misuse of tiratricol (3,5,3’-triiodothyroacetic acid) can also cause abnormal TFT. Tiratricol, an analogue of T3, is used in the treatment of thyroid hormone resistance. Because of its thyromimetic activity, tiratricol is misused as a fat burner in weight reduction. Patients taking tiratricol would have low or suppressed TSH and low fT4 levels. Free T3 (fT3) levels vary because tiratricol cross-react with most of the commercial fT3 immunoassays to different degrees, leading to spurious fT3 results. Diagnosis of factitious thyrotoxicosis may not be straightforward, especially in patients with co-existing thyroid diseases. Correct diagnosis depends on clinical vigilance, the proper use of laboratory toxicology service and correct interpretation of laboratory results.
Apart from thyroid tissues, the slimming products taken by these two patients were adulterated with sibutramine and caffeine, which might have contributed to their clinical symptoms. Sibutramine is a centrally-acting appetite suppressant which inhibits the re-uptake of serotonin and noradrenaline. Although it is a prescription only medicine in Hong Kong, illicit use in over-the-counter slimming products is not uncommon. At least 17 such products were found to be adulterated with sibutramine since 2002.4

Caffeine is a methylxanthine with mild CNS stimulant effect. It is found in a wide variety of common beverages and over-the-counter medications. Caffeine, alone or in combination with other compounds like ephedra, is widely used as supplements for weight reduction. At least one fatal case of caffeine overdose resulted from the use of slimming product related has been reported.5

The two patients described in this report purchased the adulterated slimming products through the internet. The source of these products was difficult to trace. In fact, advertisements of hundreds of slimming products can be found on the internet. Most, if not all, of these products claim to contain pure herbal ingredients. However, these are often false claims. Medical practitioners must be aware of the potential problems related to the use of non-prescription slimming products and obtain a thorough drug history. In patients who present with unexplained thyrotoxicosis and other symptoms, the alleged slimming products should be collected for detailed toxicology analysis. Good communication between clinicians and chemical pathologists is also crucial as relevant clinical information aids the selection of appropriate toxicology analyses.

References

Between the period of 1 October and 31 December 2006 there were 527 cases of poisoning (excluding infective food poisoning) recorded by the Accident & Emergency Departments (AEDs) of six acute regional hospitals (QMH, PYNEH, UCH, PWH, PMH & TMH). The male to female ratio was approximately 4:5. The distribution of age and gender is shown in Figure 1.

Of the 527 human exposures reported, 57.9% occurred at a domestic environment. Exposures occurred in the workplace in 2.5% of cases, public area 5.1%, place of amusement 2.1%, restaurants 1.5%, schools 0.2%, and healthcare facilities 0.2%. The place of exposure for the rest of the cases (30%) was unknown.

The majority (49.3%) of poison exposures were suicidal. Accidents contributed to 13.9% of cases, which was slightly outnumbered by recreational use (drug used for its pleasurable effect) which was 14.2%. Therapeutic errors accounted for 6.6% of exposures, whereas intentional misuse (e.g. attention-seeking behaviour) constituted another 7.6% of exposures. (Figure 2)

Out of the 527 cases, a total of 909 poisoning agents were involved. Western medicines, accounting for more than 70% of all agents, remained the most common poisoning agent, followed by alcohols (11.6%), and household products (5.0%). The distribution of poisoning agents involved is shown in Figure 3. An increase in poisoning cases was noted compared to a quarterly average of 400 to 500 cases. This may be explained by the increase in poisoning with alcohols during the festive season around Christmas time.
A total of five fatalities were reported in this quarter. Two cases were intentional abuse in nature and one suicidal. The fourth fatality involved an elderly man who was found to have taken a blood thinning agent of which the source was unknown. The last case involved a man for whom the cause of death has not yet been confirmed.

Poisoning by slimming agents constituted less than 1% of cases (12 in a total of 2818) according to the data collected from July 2005 to December 2006. All victims were female. The majority of the patients (83%) belonged to the age groups between 15 and 34. Half of patients were discharged at the AED and the other half were admitted into the general ward. No admission into the intensive care unit or any fatality was reported. The distribution of poisoning agents involved is shown in Figure 4.

Although the number of poisoned cases by slimming agents was small, the figure by no means indicated that this was a trivial matter. According to the Population Health Survey 2003/04, 25.6% of females and 16.4% of males aged 15 and above reported that they had done something to lose weight or avoid gaining weight in the 12 months preceding the survey. Among those who gave positive responses, 11.0% of females and 0.8% of males actually took slimming pills for weight control or reduction. For female respondents who had taken slimming pills, the largest percentage was found in the age group of 25–34 (18.2%), followed by the age group of 45–54 (11.8%), age group of 35–44 (11.6%) and age group of 15–24 (8.0%).

The poisoned cases by slimming agents reported by the six AEDs are only tip of the iceberg among people who are on weight reduction. Medical practitioners are reminded to be vigilant particularly when exposure to slimming agents are often times under-reported by a lot of people.
A normal body weight is important for health. However, normal body weight varies among different individuals taking into account their age, gender and race. Proper method should be used to assess status of obesity which includes Body Mass Index (BMI) and waist circumference. The World Health Organization suggested that in Asian adults, the desirable BMI range should be 18.5 to 22.9 and that the waist circumference should be less than 90cm for men and 80cm for women.

Obesity is mainly caused by high energy intake and/or low energy expenditure. Effective weight management requires both dietary control and regular exercise. One should avoid high-calorie diet and the consumption of sugary and fatty food. Choose low-calorie food e.g. substituting skimmed milk for full milk, and use low-calorie cooking methods like steaming and boiling instead of deep frying. It is important that a well balanced diet should always be maintained.

Regular aerobic exercise helps us lose weight. According to the American College of Sports Medicine (ACSM), aerobic exercise is any activity that uses large muscle groups, can be maintained continuously and is rhythmic in nature. If the duration of exercise is short, the body would use glucose as the main energy source. A longer duration is needed for the body to burn off fat for energy. The ACSM suggests that 30 minutes of moderate-intensity physical activity everyday is beneficial to health. For details of recommendations on healthy diet and physical activity, please visit the website http://www.cheu.gov.hk.

It is important that one should consult his/her doctor before starting a weight reduction programme especially when it is decided to take any weight-reducing medications. Weight loss should also be aimed at a safe and healthy speed. A weight reduction of about 0.2 to 1kg weekly is recommended.

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