Case series on a diversity of illicit weight-reducing agents: from the well known to the unexpected

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

Adulteration of over-the-counter proprietary medications has been reported previously. However, to date a detailed study specifically on illicit slimming products has been lacking.

WHAT THIS STUDY ADDS

This study showed the presence of a wide variety of illicit weight-reducing agents in over-the-counter slimming products, including registered or banned drugs and pharmaceutical analogues. These products may result in significant toxicities and even mortality.

AIMS

To provide an overview of illicit weight-reducing agents found in over-the-counter slimming products ingested by poisoned patients.

METHODS

The clinical details and analytical findings of slimming products involved in poisoning cases between 2004 and 2009 were reviewed.

RESULTS

Sixty-six (including one fatal) poisoning cases were encountered. Eighty-one products were analysed and found to contain undeclared prescription weight-loss drugs, drug analogues, banned drugs, drugs used for an inappropriate indication or animal thyroid tissue, with up to six illicit agents within the same product. Many products were readily available from shops or the Internet.

CONCLUSIONS

A rich diversity of illicit, potentially harmful weight-reducing agents was found in over-the-counter slimming products.

Introduction

In seeking easier options for weight control, the public is increasingly resorting to 'quick-fix' slimming agents. As a result, a variety of proprietary products with an alleged weight-reduction effect is now available on the market. These products are often advertised to contain purely natural ingredients, hence assumed to be harmless. Moreover, they are readily available over the counter and often at a low cost.

Despite the apparent safety, adverse reactions that range from being mild to life threatening have been associated with these weight-loss products. Such products

were subsequently found to contain various illicit agents, including sibutramine and diethylpropione (undeclared prescription weight-loss drugs), fenfluramine (a banned anorectic), *N*-nitrosofenfluramine (an analogue of fenfluramine) and even animal thyroid tissue [1–5].

In recent years, illicit proprietary slimming products have also appeared on the market in Hong Kong. Such products have resulted in both morbidity and mortality. The aim of the present study is to provide an overview of the various illicit weight-reducing agents found in the slimming products that were ingested by patients of poisoning cases between 2004 and 2009.

Methods

This study was conducted retrospectively by selecting and reviewing all poisoning cases suspected to involve use of illicit slimming products that were referred to the authors' laboratory between January 2004 and December 2009. Clinical data were obtained by reviewing medical records of the patients. Information collected included the age, sex, clinical features, medical and drug history of the patient, as well as the analytical findings of the slimming products received from the patients.

The compatibility between the clinical presentation of the patient and the illicit weight-reducing agent(s) found in the patient's slimming product(s) was assessed according to known side-effects of the agents, as well as circumstantial evidence, such as temporal sequence or presence of other predisposing factors of the toxicity. In cases where the clinical presentation of the patient was compatible with the illicit ingredient(s), the severity of the poisoning was graded according to a previously published system [6].

Specimens of slimming products were analysed qualitatively by the laboratory using various techniques, including high-performance liquid chromatography with ultraviolet detection, gas chromatography mass spectrometry or liquid chromatography tandem mass spectrometry (LC-MS/MS). The detection of animal thyroid tissues entailed microscopic analysis, immunoassay and LC-MS/MS analysis following protein digestion.

This retrospective study has been approved by the Hong Kong Hospital Authority Kowloon West Cluster Clinical Research Ethics Committee (KW/EX/09-128); the Committee exempted the study group from obtaining patient

consent because the presented data are anonymous and the risk of identification is low.

Results

Between January 2004 and December 2009, a total of 66 poisoning cases suspected to involve illicit slimming products were referred to the authors' laboratory. Of the 66 patients, 57 (86%) were females. The age ranged from 3 to 71 years, with a median of 25 years.

Review of clinical records and analytical findings showed that in 31 (47%) of the cases, the clinical presentation of the patient was compatible with the illicit ingredient(s) found in the patient's slimming product(s). The side-effects associated with each illicit ingredient are detailed in Table 1. Of these 31 related cases, the severity of the poisoning is as follows: fatal ($n = 1$); severe ($n = 8$); moderate ($n = 3$); and minor ($n = 19$).

From the 66 patients, 81 slimming products were received. The sources of the slimming products include the Internet, over the counter, mainland China, friends, local slimming centres or herbalist. Analysis of the slimming products demonstrated the presence of 12 ingredients that were considered to be of an illicit nature. These illicit agents could be classified into the following five categories: (i) undeclared weight-loss drugs; (ii) drug analogues; (iii) banned drugs; (iv) drugs used for an inappropriate indication; and (v) thyroid hormones. Details of each category and illicit agent, as well as the associated adverse effects, are given in Table 1.

The presence of a combination of illicit agents within the same slimming product was frequently observed. Of

Table 1

An overview of the various illicit agents detected in patients' slimming products and the associated adverse effects

Category	Illicit agent	Mode of action	Number of cases	Number of products	Associated adverse effects*
Undeclared weight-loss drug	Sibutramine	Appetite suppressant	53 (80%)	59 (73%)	Palpitation (10), tremor (4), insomnia (2), dizziness (2), myocardial infarction (1), supraventricular tachycardia (1), hypertension (1), generalized weakness (1), sweating (1)
	Mazindol	Appetite suppressant	1 (2%)	2 (2%)	Nil
Analogue	<i>N</i> -Desmethyisibutramine	Appetite suppressant	3 (5%)	4 (5%)	Supraventricular tachycardia (1)
	<i>N</i> -Bisdesmethyisibutramine	Appetite suppressant	3 (5%)	4 (5%)	Supraventricular tachycardia (1)
	<i>N</i> -Nitrosofenfluramine	Not applicable	3 (5%)	3 (4%)	Liver failure (1)
Banned drug	Fenfluramine	Appetite suppressant	12 (18%)	13 (16%)	Pulmonary hypertension (2), aortic regurgitation (1), secondary moderate tricuspid regurgitation (1), right ventricular failure (1), right heart failure and succumbed (1)
	Phenolphthalein	Laxative	22 (33%)	27 (33%)	Hypokalaemia (1), diarrhoea (1)
Inappropriate indication	Anthraquinones	Laxative (herbal)	36 (55%)	44 (54%)	Precipitate NSAID-related acute renal failure (1)
	Bisacodyl	Laxative	1 (2%)	1 (1%)	Nil
	Hydrochlorothiazide	Diuretic	1 (2%)	1 (1%)	Nil
	Spironolactone	Diuretic	1 (2%)	1 (1%)	Nil
Thyroid hormones	Animal thyroid tissue	Increase metabolism and loss of lean body mass	19 (29%)	20 (25%)	Subclinical thyrotoxicosis (7) Clinical thyrotoxicosis (9): thyrotoxic periodic paralysis (1), irritability (1), palpitation (7), tremor (6)

*Number of occurrences is given in parentheses.

Table 2

The combinations of illicit agents detected within the same slimming product

Number of illicit agents	According to mode of action	According to illicit agent
Two (n = 39)	1 × appetite suppressant + 1 × laxative (n = 27) 1 × appetite suppressant + 1 × thyroid hormone (n = 9) 2 × laxatives (n = 2) 1 × appetite suppressant + 1 × diuretic (n = 1)	Sibutramine + anthraquinones (n = 13) Sibutramine + phenolphthalein (n = 9) N-Bisdesmethyisibutramine + anthraquinones (n = 2) N-Desmethyisibutramine + anthraquinones (n = 1) Fenfluramine + anthraquinones (n = 1) Fenfluramine + phenolphthalein (n = 1) Sibutramine + animal thyroid tissue (n = 9) Phenolphthalein + anthraquinones (n = 1) Anthraquinones + bisacodyl (n = 1) Sibutramine + spironolactone (n = 1)
Three (n = 12)	1 × appetite suppressant + 2 × laxatives (n = 6) 1 × appetite suppressant + 1 × laxative + 1 × thyroid hormone (n = 5) 2 × appetite suppressants + 1 × laxative (n = 1)	Sibutramine + phenolphthalein + anthraquinones (n = 6) Sibutramine + phenolphthalein + animal thyroid tissue (n = 3) Fenfluramine + anthraquinones + animal thyroid tissue (n = 2) Sibutramine + fenfluramine + anthraquinones (n = 1)
Four (n = 7)	2 × appetite suppressants + 1 × laxative + 1 × thyroid hormone (n = 2) 3 × appetite suppressants + 1 × laxative (n = 2) 2 × appetite suppressants + 2 × laxatives (n = 1) 1 × appetite suppressant + 2 × laxatives + 1 × thyroid hormone (n = 1) 1 × appetite suppressant + 1 × laxative + 1 × thyroid hormone (n = 1)	Sibutramine + fenfluramine + phenolphthalein + animal thyroid tissue (n = 2) Sibutramine + N-desmethyisibutramine + N-bisdesmethyisibutramine + anthraquinones (n = 2) Sibutramine + mazindol + phenolphthalein + anthraquinones (n = 1) Fenfluramine + phenolphthalein + anthraquinones + animal thyroid tissue (n = 1) Fenfluramine + N-nitrosofenfluramine + anthraquinones + animal thyroid tissue (n = 1)
Five (n = 1)	2 × appetite suppressants + 2 × laxatives + 1 × diuretic (n = 1)	Sibutramine + mazindol + phenolphthalein + anthraquinones + hydrochlorothiazide (n = 1)
Six (n = 2)	2 × appetite suppressants + 2 × laxatives + 1 × thyroid hormone (n = 2)	Sibutramine + fenfluramine + N-nitrosofenfluramine + phenolphthalein + anthraquinones + animal thyroid tissue (n = 2)

the 81 specimens, the number of specimens containing one or a combination of illicit agents was as follows: one illicit agent (n = 20, 25%); two agents (n = 39, 48%); three agents (n = 12, 15%); four agents (n = 7, 9%); five agents (n = 1, 1%); and six agents (n = 2, 2%). Details of the various combinations observed are shown in Table 2.

Discussion

The present study is, to the authors' knowledge, the largest case series thus far that reports a wide diversity of illicit agents detected in a variety of proprietary weight-loss products, some of which have resulted in significant toxicities and even death. Sibutramine was the most commonly encountered illicit agent in the present study. Consistent with previous reports [4, 7], cardiovascular effects were frequently observed. In particular, myocardial infarction has been reported in patients having ingested sibutramine or other appetite suppressants [8], and this was also observed in the present case series in a patient having consumed sibutramine-containing products.

Adulteration with drug analogues has previously been reported [1, 9]. N-Nitrosofenfluramine has been associated with numerous cases of liver injury, some resulting in fulminant hepatic failure requiring liver transplant (as was the case described presently) and even death [1]. The pharma-

cological actions of sibutramine are predominantly mediated by its active metabolites, N-desmethyisibutramine and N-bisdesmethyisibutramine [7]. Hence, it was not surprising that these two analogues have also been used as adulterants in slimming products.

Phenolphthalein, a laxative that was withdrawn due to potential carcinogenicity, was found in illicit weight-loss supplements both in the present study and in previous studies [10]. Likewise, despite being banned, fenfluramine has been frequently encountered as an adulterant. In the present study, two patients had significant toxicities, one resulting in death, following ingestion of fenfluramine-tainted slimming products. Consistent with the reported adverse effects, both patients developed pulmonary hypertension and valvular disease [2, 10].

Laxatives and diuretics were found in illicit proprietary weight-loss products, and are presumed to decrease body weight by loss of water and bowel contents. However, these compounds do not possess a genuine or long-lasting weight-loss effect. Animal thyroid tissues were also detected, as has been reported previously [5]. Excessive consumption of thyroid hormones may cause impaired thyroid function and iatrogenic thyrotoxicosis, as was observed in the present study.

In interpreting the numerical data presented in this study, it should be noted that the values are only reflective of the specimens that were received by the laboratory

from poisoned patients. They are not intended to reflect the market trend or prevalence of an illicit agent. Moreover, reporting of each individual product has not been undertaken, since the aim of this study was to provide an overview of illicit agents observed in a wide range of products.

Alarming, the present study revealed the presence of multiple (up to six) illicit ingredients in a single slimming product, a phenomenon that could potentially lead to life-threatening drug–drug and herb–drug interactions. Furthermore, the potential toxicity may increase exponentially in patients who ingest multiple slimming products, which are each compounded from a range of active ingredients.

Another alarming phenomenon observed is the easy accessibility of the public to potentially harmful illicit slimming products. In addition to being available over the counter, illicit slimming products have become a global epidemic through Internet trade. To combat this epidemic, comprehensive analytical methods ought to be employed. In view of the increasing prevalence of analogues, broad-spectrum screening may provide more information than targeted analysis of commonly seen adulterants. Furthermore, correlation of the clinical toxicity, where possible, may guide development of specialized assays to identify illicit agents that may otherwise remain undetected, namely animal thyroid tissues.

Conclusions

A wide variety of illicit weight-reducing agents has been found in proprietary slimming products that are readily available to the public. Importantly, ingestion of these products may result in significant toxicities and even mortality.

Competing Interests

There are no competing interests to declare.

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