SHORT COMMUNICATION

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Safety and Quality Assessment of 175 Illegal Sexual Enhancement Products Seized in Red-Light Districts in Singapore

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Abstract

Background: In recent years, there has been increasing interest in the use of herbs and supplements as an alternative to drugs used for the treatment of erectile dysfunction, in order to enhance sexual performance. Over the years, adverse events associated with the consumption of natural health products for sexual enhancement and the treatment of erectile dysfunction have been reported.

Objective: The objective of this work was to assess the safety and quality of 175 sexual enhancement health products seized from makeshift stalls in red-light districts of Singapore.

Method: Seven raids were conducted by the Health Sciences Authority, Singapore, in two red-light districts in February and March 2008. 175 sexual enhancement health products seized from makeshift stalls were extracted with methanol and screened for Western drug adulterants using high performance liquid chromatography and gas chromatography-mass spectrometry. The labels and claims of the products were also evaluated.

Results: Of the 175 products evaluated, 134 (77%) were found to be adulterated with Western drugs or their analogues. Most of these 134 samples (123 [92%]) were found to be adulterated with sildenafil. The extent of adulteration of these illegal health products with Western drugs, including synthetic phosphodiesterase type 5 enzyme (PDE-5) inhibitors, and the risks of consuming such illegal sexual enhancement products are discussed in this study. Because of the scope of the raids, sildenafil was the most common adulterant found. In addition, some products were found to contain high contents of sildenafil (>100 mg) and high contents of the antidiabetic drug, glibenclamide (glyburide). The resultant severe hypoglycaemia has led to ten fatalities.

Conclusion: The presence of Western drug adulterants and their analogues in illegal sexual enhancement products seized from red-light districts in Singapore, and their often misleading labels and claims, put the health of

consumers at risk. To safeguard public health, greater public awareness of the danger of consuming such illegal products and the lack of quality control of these illegal sexual enhancement health products is important.

Background

Erectile dysfunction is a common and important medical condition. It is defined as the consistent inability to obtain or maintain an erection for satisfactory sexual relations. More than 18 million men in the US over the age of 20 years are affected by erectile dysfunction.[1] The prevalence of erectile dysfunction is strongly linked to age, cardiovascular disease, diabetes and a lack of physical activity. The US FDA-approved phosphodiesterase type 5 enzyme (PDE-5) inhibitor drugs used to treat erectile dysfunction are sildenafil (Viagra®), tadalafil (Cialis®) and vardenafil (Levitra®). Despite the wide use and effectiveness of these drugs, clinically significant adverse effects, such as headaches, facial flushing, visual disorders, and cardiovascular and other events have been reported.[2-12]

The advent of these highly successful drugs has spurred the marketing of herbal dietary supplements as 'natural' alternatives for the enhancement of sexual performance. The growing trend for consumers to turn to herbal treatment and supplements may be attributed to the assumption that 'natural means safe'; however, this is not necessarily true. Factors affecting the safety of such products include intrinsic toxicity, adulteration, substitution, contamination, misidentification, lack of standardization, incorrect preparation and/or dosage and inappropriate labelling. Adulteration of health products with synthetic PDE-5 inhibitors and their analogues, with claims to enhance sexual performance, has been reported.[13-21] More recently, four illegal sexual performance enhancement products have been reported to be adulterated with sildenafil and a very high dose of glibenclamide (glyburide).[22] These products have caused severe hypoglycaemia, leading to ten deaths (as at 31 August 2009).[23-26]

In this study, we report the findings from the screening of 175 illegal sexual enhancement health products for Western drug adulterants. These products are claimed to be natural supplements for the enhancement of sexual performance. The objective of this work is to evaluate the extent of adulteration of health products seized in red-light districts in Singapore with synthetic PDE-5 inhibitors and other drugs, and the risks of consuming such illegal sexual enhancement products.

Methods

Seven major raids were conducted by the Health Sciences Authority, Singapore, during the period between February and March 2008. The raids involved 17 makeshift stalls in the red-light districts in Singapore. Fifteen stalls were from the back lanes of Desker Road and two were from Pertain Road. 175 illegal sexual enhancement health products that were claimed to be natural supplements for the enhancement of sexual performance were seized and screened for the presence of Western drug adulterants.

Preliminary screening[27] for adulterants was carried out using high performance liquid chromatography with diode array detector (HPLC/DAD) and gas chromatography-mass spectrometry (GC/MS) with in-house and commercial drug libraries. Confirmation of the identities of the adulterants were carried out using liquid chromatography-electrospray ionization tandem mass spectrometry (LC-ESI/MS/MS). The quantification of these adulterants was conducted using HPLC/DAD and LC-ESI/MS/MS. The labels and claims on the products were also evaluated.

Results

Safety Assessment

Details of the 175 illegal health products seized and the results of the chemical analysis are presented in table I (see Supplemental Digital

Content 1, http://links.adisonline.com/DSZ/A18). The results showed that 134 samples (77%) were adulterated with Western drugs or their analogues.

Among the 134 samples found to contain Western drug adulterants, 102 samples contained only one adulterant, while 32 samples contained more than one adulterant. A majority of these samples (123 [92%]) were found to be adulterated with sildenafil. Fifteen samples were adulterated with tadalafil (11%), two samples were found to be adulterated with vardenafil (1.5%) and 27 samples contained other adulterants (20%). In addition, three analogues of PDE-5 inhibitors were also detected (piperidenafil,[19] thiosildenafil[20] and thiohomosildenafil[20]). Figure 1 summarizes the adulterants detected in the 134 adulterated samples. Eleven counterfeit drugs of the three approved PDE-5 inhibitors, Cialis®, Levitra® and Viagra® in different dosage forms and batches, had also been seized and screened for adulterants. Sildenafil was detected in all of these products. Two counterfeit products labelled as 'Cialis® Tadalafil 80 mg' and 'Cialis® 20 mg' (bottle) were not found to contain tadalafil. No vardenafil was detected in the products labelled as 'Levitra® 20'.

Sixty-five samples (53%) of the products adulterated with sildenafil were found to contain more than 100 mg/dosage unit of sildenafil (figure 2). The therapeutic dose of sildenafil (Viagra®) for erectile dysfunction is 25–100 mg taken not more than once daily. Two products, namely 'Power 1 Walnut 动力一号核桃素片' (product number 84 in table I [Supplemental Digital Content 1]) and 'Zhong Hua Niu Bian 中華牛鞭' (product number 132 in table I [Supplemental Digital Content 1]) were found to contain high doses of glibenclamide (98.9 mg/tablet and 13.1 mg/capsule, respectively. In addition, nine of the products (5%) were found to contain trace amounts of sibutramine.

Product Labels and Claims

Twenty of the products screened were targeted for use by female consumers. Among these

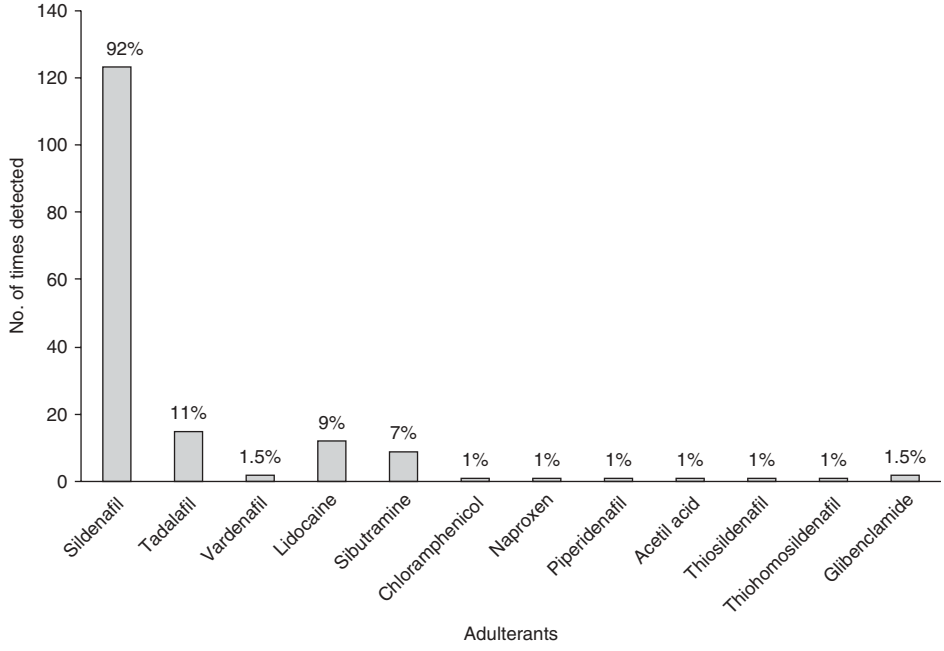

Fig. 1. No. of times (with percentage) that each adulterant was detected in the 134 samples that were found to be adulterated with Western drugs. Some samples contained more than one adulterant.

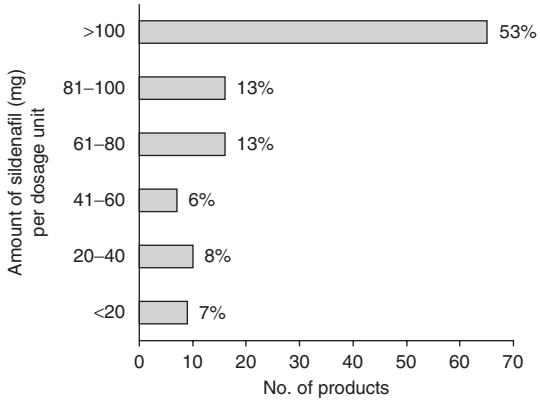

Fig. 2. Levels of sildenafil detected per dosage unit in the 123 products that were found to be adulterated with sildenafil.

products, three (15%) were found to contain lignocaine (lidocaine). Unlike those used by male consumers, most of these products (13/20 [65%]) were in solution or cream form.

Many products were claimed to be extracts of natural herbs or were produced by modern techniques. Many did not state their manufacturing dates and most had simple labels with information on indications, adverse effects and dosage. No information on drug interactions and toxicity was provided. Only a few products provided information advising consumers to consult with a physician before taking the products, and some offered 'antidotes' for adverse effects, e.g. drinking a large volume of cold water. Many products were labelled as being safe for consumers with heart disease and high blood pressure, and with concomitant consumption of alcohol.

Discussion

The easy accessibility and lower pricing of the sildenafil raw material from illegal sources may be one of the reasons for the high incidence of adulteration with sildenafil. Tadalafil and vardenafil were comparatively less frequently encountered as an adulterant in such illegal health products. In this study, 11 counterfeit products of approved PDE-5 inhibitor drugs were detected. Such counterfeit drugs were poor in quality and often contained ingredients that were different from the drugs listed on the label.

The presence of prescription drugs in such products posed a severe risk to the consumer. Consumers taking nitrate medications, such as glyceryl trinitrate (GTN), may experience a drastic drop in blood pressure if they consume such illegal health products adulterated with synthetic PDE-5 inhibitors. In addition, the high concentration of sildenafil (more than 100 mg/dosage unit) in about half of the illegal health products adulterated with sildenafil is believed to be the approach taken by dishonest manufacturers to ensure the efficacy of the products. An overdose of sildenafil and its misuse can be dangerous in view of the various adverse events reported.[2-12]

More alarmingly, the presence of glibenclamide in high doses was puzzling as well as potentially fatal. The levels of glibenclamide were 0.7–40 times above its therapeutic dose of 2.5–20 mg for daily treatment of maturity-onset diabetes mellitus.[28] Glibenclamide is a sulfonylurea antidiabetic drug that is readily absorbed from the gastrointestinal tract, with peak plasma concentrations usually occurring within 2–4 hours; it is extensively bound to plasma proteins. Glibenclamide has a relatively long duration of action of up to 24 hours, and appears to cause severe hypoglycaemia more often than shorter-acting sulfonylureas such as tolbutamide.[27] Products containing glibenclamide were responsible for the cases of severe hypoglycaemia that led to ten deaths in Singapore, as at 31 August 2009.[23-26] Pharmacologically, glibenclamide is not known to improve sexual performance and, based on the batch number of the adulterated product 'Power 1 Walnut 动力一号核桃素片', together with the period of adverse drug reaction reporting, there is a possibility that in January 2008 glibenclamide was wrongly used during the manufacturing process. From our analyses, previous batches of 'Power 1 Walnut 动力一号核桃素片' manufactured prior to 2008 were free from glibenclamide. The drug adulteration resulted in fatalities as a result of the lack of stringent good manufacturing practice that prohibits any changes of formulation according to the free will of the manufacturer. Inadequate quality control of the health products will definitely be associated with a high incidence

of health risks when these products are consumed on a regular basis.

With regard to the product label claims, many of these were incorrect, misleading and potentially dangerous to consumers. The manufacturers should bear the legal consequences of any harm to the consumers, and it is important for national authorities to collaborate and work together to curb the supply sources. One limitation is that the manufacturers listed on the labels often do not exist. The presence of lignocaine in products used by females, which were largely topical preparations for vaginal use, may be explained by the local anaesthetic effect of lignocaine to relieve pain, burning and itchy sensations during sexual intercourse.

Prior to the raids, the products were openly presented for sale at makeshift stalls in the red-light districts. After a few raids, the operators started hiding the products along drains, in beer carton boxes, etc., while some chose to display empty product boxes instead. Some products were hidden in motorcycles and were only retrieved for sale when there were interested customers. In this study, the 175 illegal sexual enhancement products were seized in seven major raids involving 17 makeshift stalls. Typically, two raids were carried out per year. In the present study, the enhanced surveillance activities were conducted as a result of the fatal hypoglycaemia cases reported. Such illegal sexual enhancement products are available worldwide and it is important to alert potential consumers, health professionals and regulators of the possibility of adulteration, counterfeiting and the presence of high levels of sildenafil and glibenclamide.

The data in this report in general may be affected by the narrow region where products were seized – all within red-light districts in Singapore. A survey that extends outside of this region, or a worldwide survey, will likely give different results and perhaps not such a preponderance of adulteration with sildenafil.

Conclusion

In conclusion, of the 175 illegal health products used for sexual performance enhancement and the treatment of erectile dysfunction that were seized in red-light districts in Singapore, 134 (77%) were found to be adulterated with Western drugs and their analogues.

In part, the extent of the adulteration explained the effectiveness of these illegal health products in sexual enhancement. Hence, with the low price and efficacy, the demand for these products remains high despite the many severe and sometimes fatal cases of adverse drug reactions reported. It is conceivable that such illegal sexual enhancement products might be effective because of the adulterant present, and not because of the pharmacognostic nature of the natural herbs. Besides, in the presence of a readily available source with an affordable price, the adulterated drug can easily be manipulated in cases of multiple health product manufacturing, which ultimately leads to severe and sometimes fatal cases of adverse drug reactions so often reported in the region.

To safeguard public health, greater public awareness of the danger of consuming such illegal products, and the lack of quality control of these illegal sexual enhancement health products, is important. An effective public education programme will help to reduce the demand of such illegal health products and complement the enforcement actions taken in the control of the supply of such illegal health products in the market. Healthcare professionals, regulators and the media play an important role in effective public education, especially in the outreach to high-risk groups, including foreign workers.

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