ORIGINAL ARTICLE

Analogues of erectile dysfunction drugs: an under-recognised threat

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Objectives To investigate the problem of drug analogue adulteration in male erectile dysfunction health products.

Design Survey of over-the-counter male erectile dysfunction health products available in convenience stores and pharmacies in Hong Kong.

Setting Tertiary referral centre for clinical toxicology analysis in Hong Kong.

Main outcome measures The pattern and extent of adulteration of male erectile dysfunction health products with sildenafil, tadalafil, and vardenafil as well as their structurally modified analogues.

Results Of 26 products studied, one (4%) was found to contain undeclared sildenafil, while 14 (54%) contained drug analogues of different kinds. The latter included acetildenafil, hydroxyacetildenafil, hydroxyhomosildenafil, and piperidenafil. The first three were analogues of sildenafil and the last was an analogue of vardenafil. One young patient presented with ataxia after taking an acetildenafil-containing product.

Conclusions The positive rate of concealed drug analogues in male erectile dysfunction health products is alarmingly high. Such analogues are difficult to detect by ordinary laboratory methods, and might be used in an attempt to evade regulatory inspection. Without going through the stringent drug testing process, the adverse effects of these chemicals remain largely unknown and unpredictable. Effective surveillance system and control measures are needed urgently. The medical profession and the public should be alerted to this under-recognised threat.

Introduction

Drug analogues are chemically modified, structurally similar compounds of existing drugs. Among other possibilities, such modifications involve the addition or deletion of one or more functional groups. Pharmaceutical companies use this strategy to produce a large number of structurally similar chemicals with the hope of finding new and better drugs.[1] Being structurally similar to the parent drug, these derivatives may retain corresponding pharmacological actions. Nevertheless, it is not uncommon for chemicals with similar structures to possess slightly or entirely different properties. Phenacetin, structurally similar to paracetamol, has been associated with renal papillary necrosis not observed with paracetamol.[2] Hence, it is prudent to test the safety and efficacy before any new chemical is licensed as drug for human use. This testing process is lengthy and costly; on average, it takes 9.5 years and costs US$802 million to license a new drug.[3]

Many drug analogues, without the aforementioned drug testing process, are available for human consumption via different channels. Examples include analogues of psychoactive drugs, anabolic steroids, and anti-obesity drugs.[4-6] Moreover, their potential adverse effects are numerous and unpredictable; in Hong Kong, a young patient presented with ataxia after taking an erectile dysfunction health product. Acetildenafil, an analogue of sildenafil, was identified. This finding triggered a local survey which revealed an alarmingly high rate of drug analogues in over-the-counter male erectile dysfunction health products.

Methods

One health product for male erectile dysfunction was obtained from a patient. Over a

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陽痿藥物的衍生物：潛藏的危機

目的 調查陽痿健康產品被摻入陽痿藥物衍生物的情況。

設計 檢驗在香港便利店和藥房出售的陽痿健康產品。

安排 香港一個毒理學分析專科轉介中心。

主要結果測量 陽痿健康產品中被摻入西地那非（又稱昔多芬，sildenafil）、他達那非（tadalafil）、伐地那非（vardenafil）及其衍生物的形式和程度。

結果 在26種產品中，一種（4%）含有西地那非，另有14種（54%）含有各類型的陽痿藥物衍生物，包括3種西地那非的衍生物acetildenafil、hydroxyacetildenafil、hydroxyhomosildenafil和伐地那非的衍生物piperidenafil。一名病人服用含有紅地那非（acetildenafil）的健康產品後出現運動失調的現象。

結論 陽痿健康產品被摻入陽痿藥物衍生物的情況極度嚴峻。一般化驗方法難以檢測到這些衍生物，相信有人藉此手段避過監管當局的藥物檢測。這些衍生物沒有經過註冊藥物所需要的安全測試，其不良後果未明，也無從預測。建立有效的監測系統及控制措施實在是刻不容緩。醫學界和市民大眾對這個被忽視的危機必須提高警覺。

period of 6 months, another 25 similar products were bought over-the-counter from local convenience stores and pharmacies. The products were tested for adulteration with sildenafil, tadalafil, and vardenafil as well as some of their structurally modified analogues, making use of previously published methods.[7] Initial screening was performed by an in-house high performance-liquid chromatography (HPLC).[8] The HPLC findings were then confirmed using liquid chromatography-tandem mass spectrometry.

Case report

A 28-year-old, previously healthy man presented with unsteady gait and frequent falls for 1 week. There was no family history of neurodegenerative disorder. On examination, he was completely normal neurologically, except that imbalance was revealed by the heel-to-toe walking test and unsteadiness was observed when standing with legs close together. Computed tomography of the brain was normal. His symptoms spontaneously improved substantially a day after admission. Review of his medications revealed that he had taken a health product for 8 consecutive days before the symptoms appeared. The product was available over-the-counter in a local convenience store, with a claim that it contained an array of natural herbal substances for improving sexual functions. Drug-related ataxia was thus suspected. Chemical analysis of this health product found acetildenafil, an analogue of sildenafil.

Local survey

To investigate the extent of drug analogue adulteration in male erectile dysfunction health products, all available over-the-counter male erectile dysfunction health remedies in a number of local convenience stores and pharmacies were purchased. A total of 25 products were acquired. All of them claimed to contain only herbal ingredients. Chemical analysis showed that one (4%) contained sildenafil, while 14 (54%) contained drug analogues of different kinds (Table). The drug analogues detected included acetildenafil, hydroxyacetildenafil, hydroxyhomosildenafil, and piperidenafil. The first three are analogues of sildenafil and the last one is a derivative of vardenafil (Fig).

Discussion

Sildenafil (Viagra; Pfizer, New York, US), tadalafil (Cialis; Eli Lilly, Indianapolis, US), and vardenafil (Levitra; Bayer Pharmaceuticals Co, Wuppertal, Germany) are the only three phosphodiesterase-5 (PDE5) inhibitors licensed for the treatment of erectile dysfunction in Hong Kong. They produce vascular smooth muscle relaxation, promote penile blood flow, and hence, induce erection. Nausea, headache, facial flushing, and visual disturbances are documented side-effects, but serious cardiovascular adverse effects have also been reported.[9] Moreover, concomitant use of medications containing nitrate may drastically lower blood pressure.[10] Ironically, ataxia is not one of the documented side-effects of PDE5 inhibitors. The latter drugs are prescription-only medicines in Hong Kong and must be used under medical supervision.

The introduction of PDE5 inhibitors was associated with a proliferation of herbal products purporting to enhance male sexual function.[11] However, some of these 'natural' products contain concealed substances, which are structurally modified analogues of the PDE5 inhibitors.[7,12,13]

Unlike the parent pharmaceutical, no formal studies have been performed to assure the safety and efficacy of these analogues. Their producers appear to trust that such analogues have clinical effects (and toxicity) similar to those of the corresponding parent compounds. This assumption is not always correct. For example, methylenedioxymethamphetamine (ie Ecstasy), an analogue of amphetamine, is associated with a higher frequency of serotonin syndrome and symptomatic hyponatremia.[14] N-nitrosofenfluramine, an unregistered analogue of fenfluramine, causes fatal hepatic failure not observed with the parent drug.[15,16] Evidently, the adverse effects of drug analogues are highly unpredictable and the consumption of such products is dangerous.

New drugs must undergo extensive testing before being marketed for human use. The testing

TABLE. Survey findings of male erectile dysfunction health products

Product No.	Proprietary name	Listed ingredients	Laboratory findings
1	Power 58 轟天炮	勃起樹根，透納樹葉，洋菝葜，瓜拉那，蒲公英，鋸棕櫚，印度精樹根，印度陽起樹根	Acetildenafil
		不含Sildenafil	
2	Enhanix 來康力	蠔精華，印度陽起樹根，透納樹葉，鋸棕櫚	Acetildenafil
		不含Sildenafil	
3	Jolex 壯力仕	納米馬格，印度精樹根，印度陽勁石	Piperidenafil
		不含Sildenafil	
4	Power 58轟天炮（白金裝）	蠔精華，樹皮，透納樹葉，印第安人參，瓜拿納，南瓜子，洋菝葜，勃起樹根	Acetildenafil
		不含Sildenafil	
5	溫養ONYO錠劑	鰻魚精，綠藻，野山人參，粗鹿角	Acetildenafil
			Piperidenafil
6	縱橫天下	馬格	Acetildenafil
7	勃樂	人參果，蟲草，紅景天浸膏粉，澱粉，微晶纖維素	Hydroxyhomosildenafil
8	皇力	鹿角，龜板，枸杷子，人參，肉蓯蓉	Hydroxyacetildenafil
9	天力	鹿角，龜板，肉蓯蓉，枸杞子，人參	Hydroxyacetildenafil
10	火龍	冬蟲夏草，人參果	Hydroxyhomosildenafil
11	Enhanix特強來康力	蠔精華，勃起樹根，鋸棕櫚，透納樹葉，印度春起草	Piperidenafil
		不含Sildenafil	
12	Power 58轟天炮金裝特強版	勃起樹根，透納樹葉，洋菝葜，瓜拉那，蒲公英，鋸棕櫚，印度精樹根，印度陽起樹根，印度春起葉	Piperidenafil
13	Power 58轟天炮白金裝特強版	蠔精華，樹皮，透納樹葉，印第安人參，瓜拿納，南瓜子，洋菝葜，勃起樹根，印度春起葉	Piperidenafil
14	Satis 神力仕	勃起樹根，蠔精華，秘魯人參，刺蒺藜，鋸齒棕櫚，燕麥	Piperidenafil
15	三體牛鞭勃動力*	黃牛鞭，鹿茸，人參，五味子，枸杞子，兔絲子，淫羊藿，肉蓯蓉，龍眼肉	Sildenafil
16	-	東革阿里	Negative
17	-	東革阿里	Negative
18	-	馬格	Negative
19	-	海狗精華，孵卵精華，南美勃起樹，黑蜂幼蟲尾	Negative
20	-	巴西人參，合歡根萃取物，螺旋藻	Negative
21	-	人參，畢茇，陽起石，淫羊藿	Negative
22	-	人參，淫羊藿，破故紙，巴戟天，花旗參	Negative
		不含西藥	
23	-	秘魯人參，威力根精華	Negative
24	-	冬蟲夏草，淫羊藿，西洋參	Negative
25	-	高麗參，阿膠，肉从蓉，鎖陽，益智，巴戟天，防風，野山人參，冬蟲夏草，淫羊藿	Negative
		不含Sildenafil	
26	-	海狗腎，鹿茸，冬蟲夏草，金銀花，高麗參，海馬，水，碘	Negative

* **This product is a registered drug and is not an analogue**

process can be broadly divided into preclinical and clinical phases. The preclinical phase begins with cell culture studies and animal experiments designed to assess target organ toxicity, teratogenicity, and carcinogenicity. Clinical testing is only allowed when these studies have been carefully conducted and the chemical is concluded to be safe. The clinical testing process is divided into three phases. Phase I studies start with small escalating doses of the drug to look for possible dose-dependent adverse reactions in human volunteers. Phase II non-blinded studies are then performed on a small number of patients (200-400) to identify an effective dose. This is followed by phase III (usually blinded) studies on a larger number

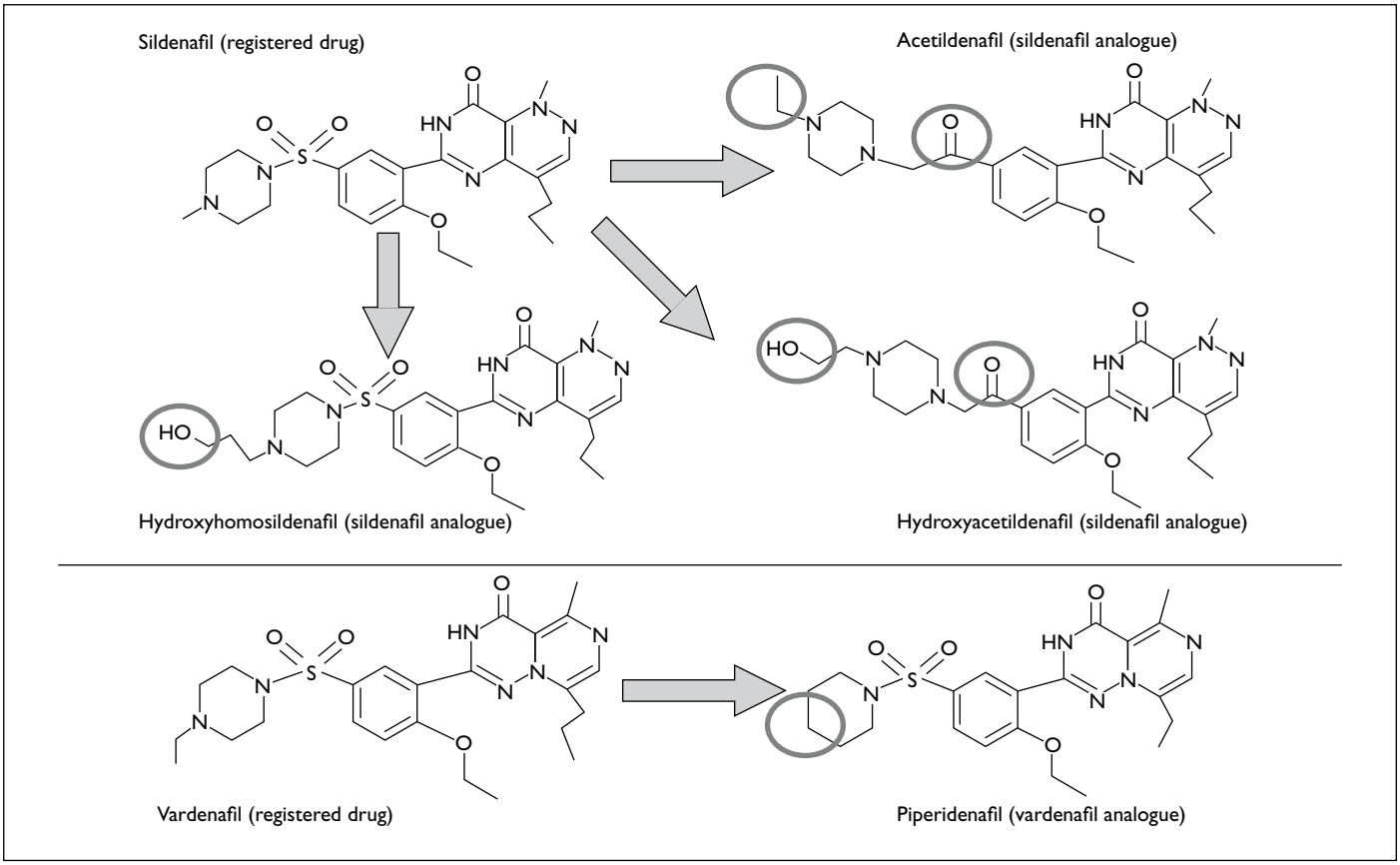

FIG. Erectile dysfunction drug analogues identified

of patients (approximately 2000) to compare efficacy against established treatment options (or placebo sometimes). Phase III trials are very expensive, time-consuming, tedious, and difficult to run. A drug is marketed for human use only after it is proven satisfactory in the above-mentioned trials.

Nonetheless, clinical trials prior to marketing are only capable of identifying adverse reactions with incidence rates of 1 in 1000 or more.[17] In theory, post-marketing safety surveillance is an integral part of the drug testing process to detect rare or long-term adverse effects in a much larger patient population. Such adverse effects may result in the withdrawal or restriction of a drug. Thus, the cardiovascular toxicity associated with rofecoxib was only discovered after the drug was marketed and used by a large number of patients.[18] Such post-marketing surveillance may be mandated by regulatory authorities or undertaken voluntarily by the drug company.

Acetildenafil is a drug analogue of sildenafil. There is no report of toxicity associated with this analogue in the literature. This does not imply that it is safe. On the contrary, the associated risk is unpredictable. The spirit of the drug testing process is that a compound must be thoroughly tested and proven to be safe and effective before it is introduced for human use. Acetildenafil has not undergone any formal animal and human trials, not to mention post-marketing surveillance. It remains speculative as to whether the ataxia observed in our index patient had a causal relationship to its use. Sildenafil has highly selective PDE5 inhibitory activity, but PDE in the nervous system is not inhibited.[19] Modifying the structure can potentially change the specificity of a drug and lead to unanticipated neurological problems.[20]

Creating drug analogues for unregistered use is an old problem. For example, analogues of anti-obesity drugs have been found to be incorporated in over-the-counter slimming products in Hong Kong.[21] Erectile dysfunction drug analogues are merely new comers. We believe that adulteration of a health product with a drug analogue instead of the parent compound amounts to an attempt to evade regulatory inspection.[22] Since analogues are structurally modified, these chemicals would be difficult to detect by ordinary laboratory methods. Additionally, the analogue is not difficult to create, which is amply demonstrated by the rich variety of such products discovered in our local survey. Once the presence of a drug analogue is exposed, it becomes 'obsolete' but can be readily replaced by others. Thus, our laboratory's initial survey findings incriminated six brands of male erectile dysfunction

health products containing acetildenafil, which were then withdrawn from the market.[23] However, a few weeks later one of the brands reappeared in some convenience stores, whereupon analysis revealed the presence of piperidenafil instead. Our findings indicate that the drug analogue problem is common, persistent, and protean.

Distressingly, erectile dysfunction drug analogues are not regarded as pharmaceuticals in Hong Kong. Their use in health products is therefore not controlled by the relevant local legislation. On the contrary, many countries have taken steps to ban these analogues.[20-22]

The threat posed by the covert use of analogues is obviously under-recognised in our society. For which reason, it is critical to introduce an effective surveillance system and control measures to tackle the problem. In Hong Kong, psychoactive designer drugs are controlled much more tightly. Analogues of the latter (having similar chemical structure) are also considered as psychoactive drugs and regulated accordingly. We advocate the same principle be applied to unregistered analogues of all other drug classes. Compulsory disclosure of all active ingredients in over-the-counter health products should be considered. Regular surveillance of high-risk products is necessary and screening should be extended to cover the registered pharmaceuticals as well as their likely analogues. While the legal loophole involving unregistered analogue use remains uncorrected, the public and the medical professionals should be alerted to this under-recognised hazard.

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