ORIGINAL ARTICLE

Outbreak of hypoglycaemia: sexual enhancement products containing oral hypoglycaemic agent

CME

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Objectives To describe a cluster of Hong Kong subjects with hypoglycaemia, after they had taken various non-prescription sildenafil products containing glibenclamide.

Design Retrospective study.

Setting A tertiary referral centre for clinical toxicology analysis in Hong Kong.

Patients All men referred to the laboratory for investigation of suspected drug-induced hypoglycaemia from December 2007 to September 2008.

Main outcome measures The characteristics of these patients, including their clinical presentations, outcomes, drug history, urine toxicology analysis results, and in some instances, analysis results of unused products.

Results A total of 144 male patients were referred for suspected drug-induced hypoglycaemia. Sildenafil and glibenclamide, or their metabolites, were detected in the urine specimens of 68 (47%) patients, none of whom had been prescribed either drug by a registered medical practitioner. Among these subjects, 24 (35%) denied any use of sexual enhancement products despite repeated questioning. Eight patients had repeated exposure resulting in re-admission. The sources of these sexual enhancement products included pharmacies in Mainland China, friends, local pharmacies, peddlers, or were unknown. Three patients died, one remains in a vegetative state and one suffered cognitive impairment; the remaining 63 recovered fully. Twenty-five unused sexual enhancement products of seven different kinds were recovered for analysis. The median (range) of sildenafil and glibenclamide per unit dose was 64 (0.05-198) mg and 70 (0-158) mg, respectively.

Conclusion These illegal products pose a severe and continued threat to society and therefore deserve widespread vigilance, so that such products can be eradicated at their source.

Key words
Drug contamination; Erectile dysfunction; Hypoglycemia; Non-prescription drugs

Hong Kong Med J 2009;15:196-200

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Introduction

The introduction of sildenafil for the treatment of erectile dysfunction has been associated with a proliferation of non-prescription products purporting to enhance male sexual function.[1] Some of which contained sildenafil or its chemical analogues which have never been registered as drugs.[2] Despite their continued availability and use, major adverse event associated with such products have never been reported.

Drug-induced hypoglycaemia is a common clinical problem. Diagnosing concealed or unintentional use of sulphonylurea, however, can be difficult. We have developed a qualitative urine assay to diagnose this causation and provided this service to all the public hospitals in Hong Kong (used by about 93% of the population).[3] Since December 2007, glibenclamide, a sulphonylurea, was detected in the urine samples of a number of male hypoglycaemic patients who denied using any drug. Subsequently, one such patient (admitted on 25 January 2008) disclosed that he had taken a non-prescription erectile dysfunction capsule. The Hospital Authority Toxicology Reference Laboratory detected sildenafil and glibenclamide in an unused capsule he had retained. This finding triggered a review of the glibenclamide-induced male hypoglycaemia cases; sildenafil, or its metabolites, were found in the urine specimens of many patients. This risk has

TABLE 1. Clinical summary of 68 patients

Clinical summary	No. of patients
No. of admissions	
1	60
2	7
3	1
Clinical presentation*	
Coma	39
Convulsion	2
Confusion	18
Right orbit fracture	1
Cerebral oedema	2
Pneumonia	1
Lightheadedness	7
Sweating	6
Drowsiness	11
Others†	5
Outcome	
Fully recovered	63
Vegetative state	1
Cognitive impairment	1
Died	3
Erectile dysfunction product taken	
Nangen Zengzhangsu "男根增長素"‡	12
Jiu Bian Wang "九鞭王"‡	5
Lu Quan "鹿泉"‡	2
San Bian Wan "三鞭丸"‡	1
One yellow capsule known as "fake Viagra"	1
Unnamed red-yellow capsule‡	9
Unnamed brick red rhomboid tablet‡	8
Unnamed blue rhomboid tablet‡§	1
Unnamed red-black capsule	1
Herbal aphrodisiac wine	1
Could not be clarified due to in coma	2
Denied	25

* Data based on the presentation for each admission. Some patients presented more than once, not necessarily with the same symptom

† Others include decerebrate posture, status epilepticus, transient left-sided weakness, slurred speech, and head injury

‡ Erectile dysfunction product available for analysis

§ Taking any erectile dysfunction product at the second admission was denied by a patient

been repeatedly communicated to local health care professionals and to the general public. However, similar cases have continued to be encountered, and the problem is still ongoing at the time of writing this report. Similar incidents were also discovered in Singapore and Japan. This report describes the cluster of cases in Hong Kong.

含降糖藥物的壯陽成藥導致血糖過低症的爆發

目的 描述一系列在香港發生，因服用含格列本（glibenclamide）的未經處方西地那非（又稱昔多芬sildenafil）產品後出現的聚集性血糖過低症。

設計 回顧研究。

安排 香港一個毒理學分析專科轉介中心。

患者 在2007年12月至2008年9月期間，因被懷疑由藥物引發血糖過低症而被轉介至化驗所的男性病人。

主要結果測量 有關患者資料，包括臨床表現、治療效果、用藥歷史、尿液樣本的毒理學化驗結果及部份藥物的分析結果。

結果 共144名男性病人因被懷疑由藥物引發血糖過低症而被轉介，當中68名（47%）病人在尿液樣本中發現的西地那非及格列本（或其代謝物）均未經處方。經多番查問，24名（35%）患者仍否認曾服食壯陽成藥。8名病人因重複服食而須再度入院。這些壯陽成藥的來源包括國內藥房、朋輩、本地藥房、小販或不知名者。當中3名病人死亡，1名仍處於「植物人」狀態，另外1名認知功能受損；其餘63名病人已完全康復。在7種壯陽成藥合共25個樣本之中，每劑量含西地那非及格列本的中位數分別為64（介乎0.05-198）毫克及70（介乎0-158）毫克。

結論 非法壯陽藥物對社會構成嚴重且持續的禍害，公眾應提高警覺，亦必須打擊違禁壯陽成藥的販賣者。

Methods

All male patients who were referred to the Hospital Authority Toxicology Reference Laboratory for investigation of suspected drug-induced hypoglycaemia between December 2007 and September 2008 were reviewed. All specimens for toxicology studies were analysed in stages by various techniques. The initial screen entailed an in-house liquid chromatography–tandem mass spectrometry to detect sulphonylureas in urine samples. Urine specimens found to have glibenclamide, or its metabolites, were additionally analysed for sildenafil and its metabolites by established methods.[4,5] A detailed drug history was obtained by reviewing the medical record, discussion with the attending clinician, and telephone interview the patient by staff in the Laboratory. Any unused erectile dysfunction products retained by these patients were collected and quantitatively analysed for sildenafil and glibenclamide. This study was approved by the local ethics committee.

Results

A total of 144 male patients were referred to the

TABLE 2. Non-prescription erectile dysfunction products collected from 14 patients

Product name	Appearance	Patient serial No.	Source	Drug amount (mg)	
				Sildenafil	Glibenclamide
Nangen Zengzhangsu "男根增長素"	Red-yellow capsule	34	China pharmacy	8.6	145
		34	China pharmacy	8.7	136
San Bian Wan "三鞭丸"	Brick red rhomboid tablet	32	China pharmacy	127	0
		32	China pharmacy	118	0
Unnamed product without packaging	Red-yellow capsule	16	Not disclosed	8.2	143
		12	Local pharmacy	7.7	133
		24	Friend	9.1	158
		24	Friend	7.9	138
		42	Friend	6.2	121
Jiu Bian Wang "九鞭王"	Brick red rhomboid tablet	33	Friend	144	0
		33	Friend	66	67
		36	Friend	64	64
		38	Peddler	63	62
Unnamed product without packaging	Brick red rhomboid tablet	47	China pharmacy	78	78
		47	China pharmacy	88	80
		47	China pharmacy	142	0
		47	China pharmacy	160	0
		47	China pharmacy	198	0
		67	Peddler	68	76
Unnamed product with packaging	Blue rhomboid tablet	39	Friend	70	73
		39	Friend	76	79
		39	Friend	72	71
Lu Quan "鹿泉"	Red-yellow capsule	65	China pharmacy	0.05	0
		65	China pharmacy	0.05	0
		68	China pharmacy	8.7	136

Laboratory for investigation of suspected drug-induced hypoglycaemia during the study period. Seventy patients did not have glibenclamide in their urine specimens. The urine of six patients contained glibenclamide but not sildenafil. The sources of glibenclamide included drug administration error (n=1), mistakenly taking medication of a family member (n=1), taking stock medication by mistake (n=1), taking Chinese proprietary diabetic medicine adulterated with glibenclamide (n=1), and unknown (n=2). The remaining 68 patients had sildenafil and glibenclamide, or their metabolites, detected in urine specimens. Eight patients had repeated exposure resulting in re-admission, despite advice against use of these products; one was admitted three times (Table 1). These 68 patients had a median age of 72 years (range, 39-87 years), and presented to 14 local public hospitals. Only one patient had a history of diabetes mellitus, whereas none had been prescribed glibenclamide or sildenafil. Table 1 summarises their clinical features. Three patients died, and as of now one remains in a vegetative state and one has suffered permanent cognitive impairment. The remaining 63 patients have recovered completely.

After repeated questioning, 38 (56%) of these patients admitted taking non-prescription erectile dysfunction products before admission. The sources of such products included: friends (n=17), pharmacies in Mainland China (n=10), local pharmacies (n=3), Mainland China peddlers (n=2), local peddlers (n=4), or unknown (n=2). Suspicious capsules were discovered in the possessions of the three (4%) deceased patients. These were retained by the regulatory authority pending forensic analysis. The two patients with impaired consciousness/cognition could not give any history; the remaining 25 (37%) denied use of any potency-enhancing drugs or herbal medicines despite repeated questioning.

A total of 25 unused products of seven different kinds were collected from 14 patients (Fig, Tables 1 and 2). The appearance of some products was similar to others with a different name (Fig). The median content of sildenafil and glibenclamide per unit dose was 64 mg (range, 0.05-198 mg) and 70 (0-158) mg, respectively (Table 2). One patient claimed to

have used a yellow capsule known as "fake Viagra" and another patient denied using any drug, but took some herbal aphrodisiac wine; these two products were not available for analysis.

Discussion

Sildenafil and glibenclamide belong to different drug groups with different indications and have never been used in the same formulation. Here we present the first cluster of hypoglycaemia cases after taking non-prescription products containing both sildenafil and glibenclamide.

The recommended therapeutic dosages of glibenclamide and sildenafil are 2.5 to 15 mg daily and 25 to 100 mg daily, respectively. Quantitative analysis of the 25 unused capsules/tablets revealed a glibenclamide content of 70 (0-158) mg per product; one such capsule/tablet can cause intractable hypoglycaemia and lead to permanent neurological damage or death. In some of the products, the sildenafil content was subtherapeutic (many were <10 mg). Individuals might take more than one capsule or tablet to obtain the desired effect, thus dramatically increasing the extent of overdosing.

The presence of glibenclamide in these products remains unexplained. Glibenclamide is not known to have a potency-enhancing effect. The highly variable drug content in these products hints at a poor quality control system in their production, if indeed there was one. Error in the manufacturing process is a possible explanation of this occurrence. The simultaneous emergence of similar products (Table 2) that contain the same but bizarre formulation suggests one single source of raw materials.

Whilst only those urine samples that were positive for glibenclamide were tested for sildenafil, the possibility of undetected cases of sildenafil and other sulphonylureas was considered unlikely, as all the adulterated sexual enhancement agents analysed during the outbreak were found to contain glibenclamide as the only sulphonylurea present.

The psychology of the patients played a significant role in this outbreak. Erectile dysfunction is an embarrassing medical condition for Chinese; many affected patients are reluctant to seek medical advice. On the other hand, street market potency-enhancing 'health supplements' are cheap, 'natural', and can be acquired without a prescription, which cultivates a black-market for these products. Men taking them also tended to conceal their drug history, as observed in this cluster of cases, making diagnosis more difficult. Many of the patients admitted to using these products only after tactful interviews conducted by male physicians in the Laboratory. Among patients who denied taking these products, none had been prescribed glibenclamide or sildenafil officially, whilst urinary analysis provided strong evidence of their usage. One can also infer that many patients with milder symptoms did not seek medical advice. Moreover, the Laboratory played a mostly passive role in receiving referrals from the frontline clinicians. Hence, the scale of the problem is very likely under-represented in our sampling.

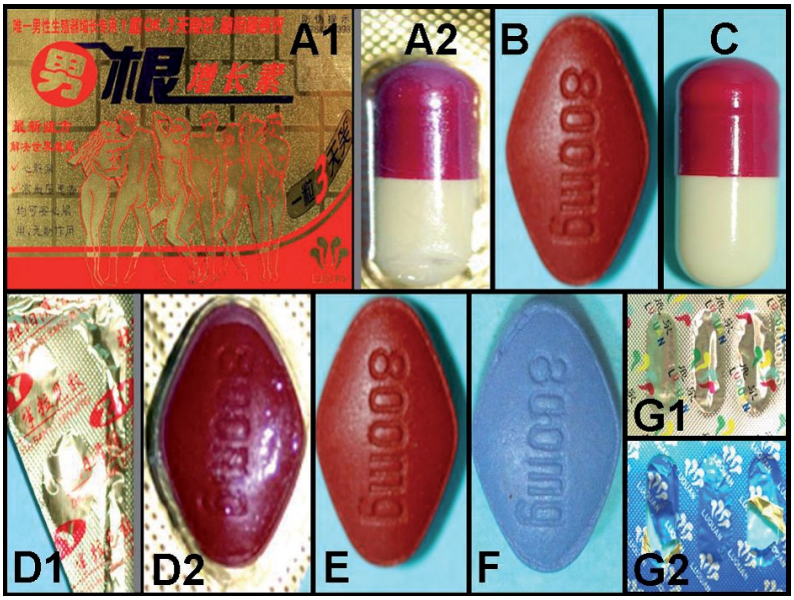

FIG. Seven non-prescription erectile dysfunction products retained by the patients
A1 and A2: the package and a red-yellow capsule of Nangen Zengzhangsu "男根增長素"; B: a brick red rhomboid tablet of San Bian Wan "三鞭丸"; C: a red-yellow capsule of an unnamed product without packaging; D1 and D2: the package and a brick red rhomboid tablet of Jiu Bian Wang "九鞭王"; E: a brick red rhomboid tablet of an unnamed product without packaging; F: a blue rhomboid tablet of an unnamed product with packaging that was the same as D1; G1: the package of Lu Quan "鹿泉" with red-yellow capsules but otherwise like C; G2: another package of Lu Quan "鹿泉" with red-yellow capsules akin to C

With the concealed drug history and the unusual co-existence of sildenafil and glibenclamide in these products, the Laboratory played a critical role in promptly defining and elucidating this outbreak. After the first case was diagnosed in January 2008, the clustering was established by demonstrating similarly affected cases within 24 hours. All the cases in this cluster were confirmed by the Laboratory. The risk was immediately publicised; a press release was issued by the local health authority to the public on the same day the clustering was confirmed, and letters were also mailed to all doctors and private hospitals as well as medicine traders to alert them of these incidents.[6] Local pharmacies and retail shops were inspected by the health authority. Among these, suspicious pills were seized from one retail shop, whose owner was arrested. The health authorities of nearby cities (Macau and Shenzhen),[6] as well as London,[7] were informed of the incidents. Two neighbouring nations, Japan and Singapore, subsequently encountered similar

cases. In Japan, where three men were hospitalised after taking "Nangen Zengzhangsu" (one of the Hong Kong products), the Ministry of Health, Labor and Welfare conducted a large-scale market surveillance. This revealed nearly 200 health products containing sildenafil or its structurally related analogues, though such contents did not appear in the product label.[8] In Singapore, multiple drug raids by the Health Sciences Authority yielded 100 000 units of similar illegal products. They included one named "Power 1 Walnut", in connection with which nine subjects were arrested.[9] The "Power 1 Walnut" pill was analysed to contain traces of sildenafil (1 mg) and significant amounts of glibenclamide (93-98 mg), which was similar to our findings. Severe neuroglycopenia, as well as brain abnormalities on imaging, were noted in patients who ingested these tablets.[10,11]

Despite repeated public warnings, similar cases have continued to occur in Hong Kong[12] and Singapore. At the time of writing, 61 confirmed and 148 suspected patients in Singapore have been identified, among whom 10 have died.[13] Most worrying of all, as of now the ultimate source of these illegal products remains unknown.

We believe the proliferation of these various erectile dysfunction products poses a severe threat to men worldwide, and warrants immediate attention and action from health authorities in different countries. We advocate prompt education of the public, which must include warnings to avoid erectile dysfunction products of dubious origin.[14] Aid from international regulatory bodies may be necessary to trace their ultimate source and eliminate these potentially lethal products.

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