Analogues of erectile dysfunction drugs: an under-recognised threat

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Methods

One health product for male erectile dysfunction was obtained from a patient. Over a
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. Initial
screening was performed by an in-house high
performance-liquid chromatography (HPLC). 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. Moreover,
concomitant use of medications containing nitrate
may drastically lower blood pressure. 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. However, some of these ‘natural’ products contain
concealed substances, which are structurally
modified analogues of the PDE5 inhibitors.

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. N-nitrosofenfluramine,
an unregistered analogue of fenfluramine, causes fatal
hepatic failure not observed with the parent drug.
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

<table>
<thead>
<tr>
<th>Product No.</th>
<th>Proprietary name</th>
<th>Listed ingredients</th>
<th>Laboratory findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Power 58 桃天炮</td>
<td>勃起樹根，透納樹葉，洋茖莢，瓜拉那，蒲公英，銀棕樹，印度綠樹根，印度黴樹根，不含Sildenafil</td>
<td>Acetildenafil</td>
</tr>
<tr>
<td>2</td>
<td>Enhance 良康力</td>
<td>蜂精華，印度綠樹根，透納樹葉，銀棕樹</td>
<td>Acetildenafil</td>
</tr>
<tr>
<td>3</td>
<td>Jolex 壯力仕</td>
<td>納米馬格，印度綠樹根，印度陽勁石，不含Sildenafil</td>
<td>Piperidenafil</td>
</tr>
<tr>
<td>4</td>
<td>Power 58 桃天炮</td>
<td>蜂精華，樹皮，透納樹葉，印度安人參，瓜拉那，瓜拉那，洋茖莢，勃起樹根，不含Sildenafil</td>
<td>Acetildenafil</td>
</tr>
<tr>
<td>5</td>
<td>溫養ONYO錠剂</td>
<td>鰻魚精，滋蔘，野山人参，鹿角</td>
<td>Acetildenafil</td>
</tr>
<tr>
<td>6</td>
<td>桃天天下</td>
<td>鹿茸</td>
<td>Acetildenafil</td>
</tr>
<tr>
<td>7</td>
<td>助樂</td>
<td>人參果，蟲草，紅景天浸膏粉，潤粉，微晶纖維素</td>
<td>Hydroxyhomosildenafil</td>
</tr>
<tr>
<td>8</td>
<td>皇力</td>
<td>鶴角，狗板，枸杞子，人參，肉蓯蓉</td>
<td>Hydroxyacetildenafil</td>
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<tr>
<td>9</td>
<td>天力</td>
<td>鶴角，狗板，肉蓯蓉，枸杞子，人參</td>
<td>Hydroxyacetildenafil</td>
</tr>
<tr>
<td>10</td>
<td>火龍</td>
<td>冬蟲夏草，人參</td>
<td>Hydroxyhomosildenafil</td>
</tr>
<tr>
<td>11</td>
<td>Enhance特強來康力</td>
<td>蜂精華，勃起樹根，銀棕樹，透納樹葉，印度陽草，不含Sildenafil</td>
<td>Piperidenafil</td>
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<tr>
<td>12</td>
<td>Power 58 桃天炮</td>
<td>勃起樹根，透納樹葉，洋茖莢，瓜拉那，蒲公英，銀棕樹，印度綠樹根，印度黴樹根，印度陽草，不含Sildenafil</td>
<td>Piperidenafil</td>
</tr>
<tr>
<td>13</td>
<td>Power 58 桃天炮</td>
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<td>Piperidenafil</td>
</tr>
<tr>
<td>14</td>
<td>Satis 永力仕</td>
<td>勃起樹根，蜂精華，秘魯人參，刺蕊薇，銀棕樹，鹿茸</td>
<td>Piperidenafil</td>
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<tr>
<td>15</td>
<td>三極牛鞭強效力</td>
<td>黃牛鞭，鹿茸，人參，五味子，枸杞子，兔肉子，淫羊藿，肉蓯蓉，鹿根肉</td>
<td>Sildenafil</td>
</tr>
<tr>
<td>16</td>
<td>-</td>
<td>東革阿里</td>
<td>Negative</td>
</tr>
<tr>
<td>17</td>
<td>-</td>
<td>東革阿里</td>
<td>Negative</td>
</tr>
<tr>
<td>18</td>
<td>-</td>
<td>马格</td>
<td>Negative</td>
</tr>
<tr>
<td>19</td>
<td>-</td>
<td>海狗精華，軟骨精華，南美勃起樹，黑蜂幼蟲</td>
<td>Negative</td>
</tr>
<tr>
<td>20</td>
<td>-</td>
<td>巴西人參，合軟根萃取物，螺旋藻</td>
<td>Negative</td>
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<tr>
<td>21</td>
<td>-</td>
<td>人參，鹿茸，陽起石，淫羊藿，鹿茸</td>
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<tr>
<td>22</td>
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<td>人參，淫羊藿，破故紙，巴戟天，花旗參</td>
<td>Negative</td>
</tr>
<tr>
<td>23</td>
<td>-</td>
<td>秘魯人參，威力根精華</td>
<td>Negative</td>
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<tr>
<td>24</td>
<td>-</td>
<td>冬蟲夏草，淫羊藿，西洋参</td>
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<tr>
<td>25</td>
<td>-</td>
<td>高麗參，阿膠，肉苁蓉，鎖陽，益智，巴戟天，防風，野生人參，冬蟲夏草，淫羊藿，不含Sildenafil</td>
<td>Negative</td>
</tr>
<tr>
<td>26</td>
<td>-</td>
<td>海狗腎，鹿茸，冬蟲夏草，金銀花，高麗參，海馬，水，胰</td>
<td>Negative</td>
</tr>
</tbody>
</table>

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

The 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...
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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{19} Modifying the structure can potentially change the specificity of a drug and lead to unanticipated neurological problems.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{25} However, a few weeks later one of the brands reappeared in some convenience stores, whereupon analysis revealed the presence of piperidinafil 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.\textsuperscript{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.

References

17. Strom BL. How the US drug safety system should be changed. JAMA 2006;295:2072-5.