VICTORY Project: a Study of Counterfeit PDE5 Inhibitor (Sildenafil) in Indonesia

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ABSTRACT

Aim: to quantify the extent of counterfeit sildenafil in Indonesia. Methods: the study was conducted in 4 big areas: Jakarta, Bandung, East Java (Surabaya and Malang), and Medan. Sildenafil 100 mg tablets were purchased from pharmacies, drugstores, street peddlers, and 3 Indonesian websites. The outlets were chosen by random sampling in each stratum (type of outlet). Sildenafil tablets purchased were sent to Pfizer Quality Operations Division, Dalian, China, for authenticity evaluations (by infra red spectral analysis). All counterfeit tablets were then sent to Pfizer Counterfeit Medicines Laboratory, Sandwich, UK, a portion of which were analyzed quantitatively for sildenafil concentration per tablet (by HPLC). Results: a total of 518 sildenafil 100 mg tablets were collected and sent to Dalian. Of these tablets, 284 tablets (55%) were genuine sildenafil and 234 tablets (45%) were counterfeit sildenafil. Counterfeit sildenafil were mostly found in street peddlers (100%), in drugstores (56%), and from internet (33%), but pharmacies also had (13%) counterfeit sildenafil. The sildenafil content of 106 counterfeit tablets analyzed varied from 24 to 157 mg per 100 mg tablet. No analysis was done to determine other active ingredient. Conclusion: 45% sildenafil 100 mg tablets in Indonesia were...
INTRODUCTION

Viagra®, the innovator of sildenafil, is a breakthrough drug in terms of its ability in oral form to help men with erectile dysfunction (ED) to obtain or maintain an erection for satisfactory sexual relations. In United States, more than 18 million men above the age of 20 years have erectile dysfunction.1

Counterfeit drugs, according to the World Health Organization (WHO), are those that deliberately and fraudulently mislabelled with respect to identity or source: their quality is unpredictable as they may contain the wrong amount of active ingredients, wrong ingredients or no active ingredients. They are manufactured in clandestine laboratories with no possibility of control.2

Sildenafil, a phosphodiesterase type 5 (PDE5) inhibitor, is an effective oral medication for ED. Other drugs of the same class with the same indication are vardenafil (Levitra®) and tadalafil (Cialis®). These drugs are prime targets for counterfeiting because of their high price and the embarrassment associated with the underlying condition. In fact, PDE5 inhibitors were the most commonly counterfeited class of product in Europe.3 Until now, sildenafil is the most commonly counterfeited drug all over the world because it is the most famous drug as the first oral anti ED. During 5 years from 2004 to 2008, 35.8 million counterfeit sildenafil tablets were seized in Europe. In 2004, law officers seized 10.6 million counterfeit sildenafil tablets, which were seven times the number of all other counterfeit Pfizer products combined.4 It was estimated that 0.6–2.5 million men in Europe could be exposed to illicit sildenafil. For comparison, IMS Health estimated the number of users of legal sildenafil in the European Union were 2.5 million in 2006.4

KEYWORDS: sildenafil, pharmacy, drug store, street peddler.

METHODS

The study was conducted in four big areas: JaBoDeTaBek (Jakarta, Bogor, Depok, Tangerang and Bekasi), Bandung, East Java (Surabaya and Malang), and Medan. Sildenafil 100 mg tablets were purchased from all types of outlets: pharmacies (ordinary, chain, and hospital), drugstores, street peddlers, and 3 different Indonesian websites. The outlets were chosen by random sampling in each stratum (pharmacies, drugstores, and street peddlers).

Sildenafil 100 mg tablets purchased were sent to Pfizer Quality Operations Division, Dalian, China, for authenticity evaluations of the sildenafil tablets. The evaluation was performed qualitatively by infra red (IR) spectral analysis. The counterfeit tablets were separated into 6 different formulations based on the IR analyses. All counterfeit tablets found were then sent to Pfizer Counterfeit Medicines Laboratory, Sandwich, UK, a portion of which were analyzed quantitatively for sildenafil content per tablet (by HPLC), and determination of its purity (% impurity).

RESULTS

From the 4 big areas, 86 pharmacies, 38 drugstores, and 30 street peddlers were chosen. From these outlets and 3 websites, a total of 518 sildenafil 100 mg tablets were purchased and sent to Dalian. Among these tablets, 284 tablets (55%) were authentic sildenafil and 234 tablets (45%) were counterfeit sildenafil.

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The authentic and counterfeit sildenafil tablets are shown in each area (Figure 1) and in each group of outlets (Figure 2).

Counterfeit sildenafil tablets were mostly found in JaBoDeTaBek (165 tablets=50%), followed by East Java (55 tablets=50%).

Counterfeit sildenafil tablets were mostly found in “illegal” outlets, especially in street peddlers (100%), and in drugstores (56%). Pharmacies also had 13% counterfeit sildenafil. Among 12 sildenafil tablets purchased from the internet, 4 were counterfeit.

The outlets with counterfeit tablets and the counterfeit tablets in each type of outlet can be seen in Table 1.

Table 1. The outlets with counterfeit sildenafil tablets

<table>
<thead>
<tr>
<th>Outlet</th>
<th>Total no. of outlets</th>
<th>No. of outlets with counterfeit tablets</th>
<th>Total no. of tablets</th>
<th>No. of counterfeit tablets</th>
<th>No. of counterfeit tablets analyzed for sildenafil content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacy</td>
<td>86</td>
<td>6</td>
<td>259</td>
<td>34 (13%)</td>
<td>9</td>
</tr>
<tr>
<td>Drugstore</td>
<td>38</td>
<td>19</td>
<td>117</td>
<td>66 (56%)</td>
<td>36</td>
</tr>
<tr>
<td>Street peddler</td>
<td>30</td>
<td>30</td>
<td>130</td>
<td>130 (100%)</td>
<td>60</td>
</tr>
<tr>
<td>Internet</td>
<td>3</td>
<td>1</td>
<td>12</td>
<td>4 (33%)</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>157</td>
<td>56 (36% of total)</td>
<td>518</td>
<td>234 (45% of total)</td>
<td>106</td>
</tr>
</tbody>
</table>

Among 234 counterfeit sildenafil tablets, 53% contained dehydrated calcium sulphate, 32% maltose dextrin, 5% lactose, 4% microcrystalline cellulose, 4% avicel PH 102 (a type of cellulose), and 2% unknown. Based on Dalian’s IR analysis, the similarity to authentic sildenafil varied from 13 to 69%.

DISCUSSION

In the present study, some sildenafil were present in every counterfeit sildenafil tablet (24–157% per 100 mg tablet). Counterfeit sildenafil tablets seized in the United Kingdom contained 40-100% sildenafil per 100 mg tablet, while in Europe between 2005 and 2009, the sildenafil content in 2383 tablets of suspect counterfeit sildenafil was 0 to >200% of the indicated strength. In the Netherlands, among 370 illegally
sold sildenafil tablets collected from 2000 to 2004, only 10 were genuine, sildenafil was often present, but in lower amounts than declared. Although the percentage of counterfeit sildenafil found in the present study was alarming (45%), there was no data on other active ingredient that might be present in it and could be hazardous or even fatal. For example, the high content of glibenclamide in counterfeit sildenafil tablets caused severe hypoglycemia in 149 nondiabetic men in Singapore between January 1st and May 26th, 2008. Seven of these men remained comatose as a result of prolonged neuroglycopenia, and four subsequently died.8 Other examples of other active pharmaceuticals in counterfeit sildenafil tablets collected from 2000-2004 in the Netherlands were amphetamine, paracetamol, metronidazole, clomiphene, chloramphenicol, dipyrone, fluoxetine, tadalafil, yohimbine, gamma-aminobutyric acid, caffeine, L-arginine, and quinine.7 Even herbal or dietary supplements that were marketed for sexual dysfunction in the US and claimed “100% natural product”, obtained over the counter or directly from the manufacturer using the internet, revealed that some of the tablets analyzed contained an average of 55 mg of sildenafil per capsule. In Singapore, among 175 illegal sexual enhancement health products that were claimed to be natural supplements for the enhancement of sexual performance, 134 tablets were found to contain Western drug adulterants, i.e. 123 tablets of these contained sildenafil, 15 tablets contained tadalafil, and 2 tablets adulterated with vardenafil.10

We do not know what other active pharmaceutical ingredients adulterating counterfeit sildenafil tablets were found in Indonesia, so that we are not able to predict the hazardous effects that may arise from these counterfeit sildenafil, not to mention the adverse drug interactions that may occur. Despite the high percentage of counterfeit sildenafil tablets (45%), no adverse events have been reported associated with it. However, this may be due to the poor adverse drug reactions reporting system in Indonesia. Also, because most counterfeit sildenafil tablets were found in illegal drug outlets (drugstores and street peddlers) and purchased by ED patients without prescription, then the adverse events, if occurred, were never reported. Only if the adverse events were severe or serious, and the subjects were admitted to hospitals, then healthcare professionals (HCPs) acknowledged the adverse events and reported them, if they were obliged to. Since this obligation does not exist, then the adverse events will not be reported and eventually forgotten, as if they never happen.

What are the theoretical hazards of counterfeit sildenafil for ED patients without prescription? It should be noted that counterfeit sildenafil often contains sildenafil, and in this study, it ranged from 23 mg to 157 mg per tablet. First of all, the contraindications of sildenafil use: (i) patients using nitrates, sildenafil will potentiate the hypotensive effect of nitrates causing severe hypotension; (ii) patients with preexisting cardiovascular disease, in whom sexual activity is inadvisable. Then, the warnings and precautions of sildenafil use: (i) age >65 years, hepatic impairment (e.g. cirrhosis), severe renal impairment (ClCr <30 mL/min) will increase plasma levels of sildenafil 40 to 100%; (ii) drug interactions with potent inhibitors of CYP3A4 (ketoconazole, itraconazole, erythromycin, saquinavir) will approximately double the plasma levels of sildenafil, while ritonavir will cause eleven-fold increase; (iii) myocardial infarction, stroke, life-threatening arrhythmias within the last 6 months; hypotension (<90/50 mmHg); hypertension (>170/110 mmHg); cardiac failure or coronary artery disease causing unstable angina.11 High plasma levels of sildenafil may cause optic neuropathy12, priapism11 (painful erections for >6 hours), besides decreased blood pressure until syncope.11 This information, known by the HCPs, but not known by users of sildenafil without prescription may endanger these users. Furthermore, men with ED commonly have comorbid conditions (e.g. hypertension, diabetes) that carry a significant risk for morbidity and mortality. Without a physician visit, these men lose the opportunity to address these underlying conditions.13

In the present study, 5.7% of the counterfeit sildenafil contained more than 105 mg of
sildenafil (until 157 mg). This high concentration of sildenafil is believed to be the approach of dishonest manufacturers to ensure the efficacy of the products.

From the fact that counterfeit sildenafil were 100% in street peddlers, 56% in drugstores, and 13% in pharmacies, then the potential consumers know where to find most likely the genuine sildenafil.

CONCLUSION

Of the 518 tablets of sildenafil 100 mg purchased from 4 big areas in Indonesia, 45% were counterfeit. The counterfeit sildenafil tablets were found in street peddlers (100%), drugstores (56%), and in pharmacies (13%), all of which contained sildenafil, ranging from 24 to 157%. No other active ingredients were sought. This report is aimed to alert the potential consumers, health professionals and regulators of this problem.

CONFLICT OF INTEREST

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REFERENCES

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