

HIGH DOSAGE SIBUTRAMINE DETECTED IN CHINESE HERBAL DRUG

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ABSTRACT

Traditional herbal remedies are being used as alternative medicine by a large proportion of people worldwide. Herbs are generally considered as safe and free of side effects, because of their natural origin.

The presented case, a 36 years old woman, had used a herbal medicine, called “Lida Dai Hua Jiao Nang” via internet for weight reduction. Although, she developed severe headache, vertigo, dyspnea, arrhythmia and sleeplessness on the second day, she kept on taking the product for ten days. However, due to worsening in symptoms, she was admitted to our hospital.

A urine sample of the case and a capsule of “LiDa” were analyzed by gas chromatography mass spectrometry (GC-MS). Sibutramine was detected in urine, which was also detected as major ingredient of “LiDa”. It was quantified as at least 22 mg in each capsule of “LiDa”.

There are lots of herbal products used for the purpose of weight loss. Due to convincing numbers reports dealing with adverse effects, sales of these kinds of products are forbidden in most of the countries. However, they are still available to consumers over the internet.

Key Words: Sibutramine, chinese herbal drug, clinical medicine, forensic toxicology. *Nobel Med 2012; 8(1): 100-102*

BİTKİSEL ÇİN İLACINDA YÜKSEK DOZDA SIBUTRAMİN TESPİTİ

ÖZET

Geleneksel bitkisel ilaçlar, dünyada yaygın bir kitle tarafından alternatif tıp olarak kullanılmaktadır. Bitkiler, doğal kaynaklı olmaları nedeniyle güvenli ve yan etkisiz olarak kabul edilmektedir.

Otuz altı yaşındaki kadın olgu internet aracılığı ile “Lida Dai Hua Jiao Nang” diye isimlendirilen zayıflatıcı bir ilaç sipariş etmiştir. İlacı almaya başladıktan iki gün sonra şiddetli baş ağrısı, vertigo, solunum sıkıntısı, aritmi ve uykusuzluk şikayetleri gelişmesine rağmen hasta ilacı kullanma-

ya on gün boyunca devam etmiştir. Ancak semptomlarının şiddetlenmesi üzerine hastanemize başvurmuştur. Hastadan alınan idrar örneği ve bir LiDa kapsülü gaz kromatografisi-kütle spektrometresi (GC-MS) ile analiz edildi. İdrarda, LiDa'nın da içindeki en önemli etken madde olan, sibutramin olduğu tespit edildi. LiDa kapsüllerinde en az 22 mg sibutramin olduğu saptandı. Zayıflama amacıyla kullanılan birçok bitkisel ürün bulunmaktadır. Söz konusu ilaçların yan etkilerini gösteren önemli miktardaki çalışma bulunması nedeniyle birçok ülkede satılmaları yasaklanmış ise de internet üzerinden hala satıldıkları bilinmektedir.

Anahtar Kelimeler: Sibutramine, bitkisel çin ilacı, klinik tıp, adli toksikoloji *Nobel Med 2012; 8(1): 100-102*

INTRODUCTION

The use of herbal drugs is becoming more common all over the world. Especially, people frequently use such herbal products for weight loss. However, these products are complex and possibly contain naturally toxic herbs. Furthermore, they might be contaminated with certain hazardous agents and might involve incorrect preparation of dosage and adulteration. Herbal drugs are generally considered to be safe and free of

adverse effects. However, many problems can arise when herbal drugs are adulterated with synthetic therapeutic substances such as metals (mercury, lead, arsenic and copper) and pharmaceuticals (antihistamines, non-steroid anti-inflammatory drug). Numerous reports dealing with adverse effects associated with herbal drugs are available¹. LiDa is a Chinese product, which is being sold as herbal or algae originated totally natural drug in the market. But, sibutramine, an active formulation used in obesity treatment, is detected to be one of the →

major ingredients of LiDa. Sibutramine is a serotonin-noradrenaline reuptake inhibitor, which is used for obesity treatment. However, sibutramine can cause side effects on the cardiovascular system and the central nervous system such as increase in blood pressure and pulse rate, chest pain and headache, paraesthesia, insomnia, dry mouth, and anxiety². In this report, we present a case admitted hospital with severe toxicity following ingestion of LiDa. Toxicological analysis of samples of urine and used herbal drug were performed by gas chromatography-mass spectrometry (GC/MS).

CASE REPORT

A thirty-six years old woman had ordered a Chinese herbal medicine, called "Lida Dai Dai Hua Jiao Nang", from internet. Following intake, she developed symptoms of severe headache, vertigo, dyspnea, aritmia and sleeplessness. Despite the symptoms, she continued to use one pill of this product for each day for 10 days, for weight reduction. Afterwards, she admitted to Emergency Service of our hospital due to elevated symptoms. During this time she had not take any other medication. Her weight was 65 kg, and upon admittance she was recorded to complain about severe headache, restlessness and palpitation with a blood pressure of 145/85 mmHg and a pulse rate of 105 per minute. A urine sample taken 6 h after the last intake and a "LiDa" capsule were analyzed by GC-MS in our Forensic Toxicology Department. LiDa use was stopped immediately and no additional treatment applied to the case. During the first day, the symptoms and complaints of the case were disappeared. Furthermore blood pressure (130/75 mmHg) and pulse rate (80/min) decreased to normal levels. And the case discharged after two days of observation.

Standard solutions were prepared using the Sibutramine Hydrochloride Monohydrate. The stock solution of sibutramine (1-(4-chlorophenyl)-N,N-dimethyl- α -(2-methylpropyl)cyclobutanemethanamine) at the concentration of 100 $\mu\text{g/ml}$ was prepared in methanol, and they were kept below 4°C until they were used. To calibrate the method, four point calibrators were tested: 0.5, 1, 2 and 4 $\mu\text{g/ml}$. Linear regression analysis of the calibration data showed a correlation coefficient $R^2 > 0.99$. Coefficients of variation (CV) three replicates per level were 0.35%, 0.78%, 1.52% and 0.86%, respectively. All of used solvents were of HPLC grade. Potassium dihydrogen phosphate (KH_2PO_4) was obtained from Sigma (Germany). Oasis MCX (3cc, 60 mg) SPE Extraction Cartridge used for sample preparation was procured from (Waters Corp., Ireland). Urine sample was analyzed with our routine laboratory drug analyzing method³. For analysis of the 'LiDa' capsule, 10 mg of each was suspended in 100 ml methanol and 0.1 ml methanol solution was analyzed by GC/MS after dilution 1/10 (v/v). An Agilent model 6890 GC and 5973 mass selective detector (USA) and

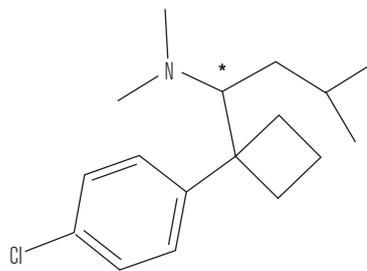


Figure 1. Molecular structure of sibutramine (1-(4-chlorophenyl)-N,N-dimethyl- α -(2-methylpropyl)cyclobutanemethanamine). *asymmetric carbon

a DB-17MS (J&W Scientific, USA, 15-m length, 0.25-mm i.d., 0.25- μm film thickness) was used. The column temperature program was as follows: 80°C, increased to 300°C at 20°C/min, and hold 300°C for 5 min. Helium was used as the carrier gas. The injection port temperature was 250°C, and GC-MS interface temperature was 280°C. Analysis was performed both in EI ionization mode. The selected ion-monitoring (SIM) mode was used. As an ingredient of the LiDa sibutramine was identified by the GC/MS library (Figure 1). The quantifying ion for sibutramine was 114 m/z. Total ion chromatogram and mass spectrum of sibutramine in LiDa capsule is shown in Figure 2 and Figure 3. The retention time was 6.05 min.

RESULTS

The urine sample of patient was analyzed by GC/MS and sibutramine, as a unique major ingredient, was detected in "LiDa" capsule. Quantification yielded by our laboratory had shown that each capsule contained at least 22 mg sibutramine, which is alarming. Comparing those medications used in obesity treatment, dosage of sibutramine in the examined Chinese drug was approximately two times higher than therapeutic level. Different results were observed for each of the weighed LiDa capsules, which meant that these drugs are not controlled or regulated in appropriate laboratory conditions.

DISCUSSION

The adulteration by synthetic therapeutic substances of traditional Chinese medicines has been reported. Huang et al reported that approximately 23.7% of 2609 samples of traditional Chinese medicines analyzed in Taiwan were adulterated with synthetic drugs of various pharmacological activities.⁴ Similarly, a study by Koh et al revealed a similar adulteration profile in Chinese herbal remedies in Singapore.⁵ A review of the literature showed that Chinese herbal products are mostly adulterated by anti inflammatory drugs, steroids, codeine, dexamethasone and phenfluramine. Due to in appropriate laboratory applications drug adulteration can have serious results. Kanda et al. diagnosed chronic hepatitis in a patient self-medicated a herbal drug containing phenfluramine during one year of use.⁶ →

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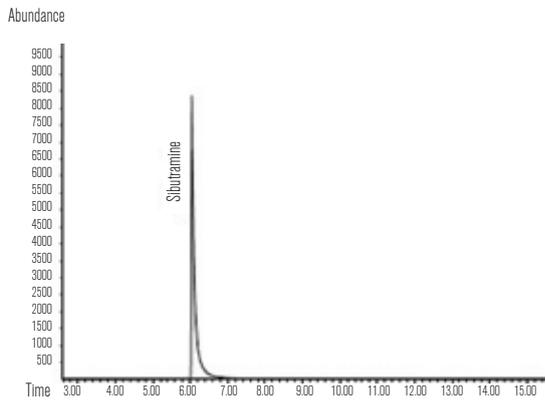


Figure 2. GC-MS chromatogram of sibutramine in herbal drug (LiDa) capsule (The total ion chromatogram frame).

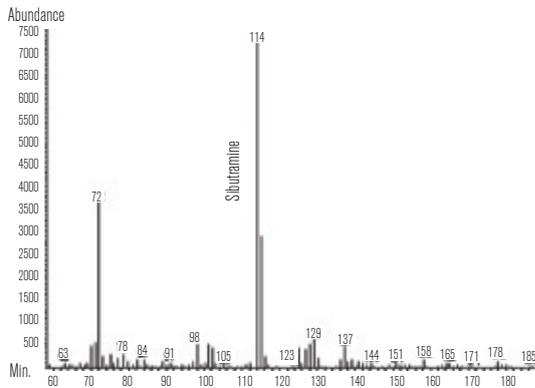


Figure 3. GC-MS analysis of sibutramine in herbal drug (LiDa) capsule (The mass spectrum frame)

Additionally, Gertner et al. described five patients with arthritis taking herbal remedies which were found to contain mefenamic acid and diazepam.⁷ Serious complications such as massive gastrointestinal bleeding occurred in these cases.

In the presented case, sibutramine was identified in Chinese herbal remedy called LiDa. Sibutramine is a synthetic noradrenaline, dopamine and serotonin reuptake inhibitor, which is used to treat obesity. The

most commonly reported adverse effects of sibutramine are headache, constipation and nausea. Certain adverse events associated with the nervous system, including dizziness, dry mouth and insomnia. Increases in blood pressure and pulse rate were possible adverse effects that require regular monitoring especially in obese hypertensive patients.² Jung et al. reported the quantity of sibutramine as 27.4 mg in LiDa capsules.⁸ Similarly, sibutramine was detected in "LiDa" capsule ordered via internet, in our case. However, quantification yielded by our laboratory revealed that each capsule of LiDa contained at least 22 mg of sibutramine, which is approximately two times higher than therapeutic level in pharmacological formulas.

Presented case demonstrates a common problem of misuse of herbal drugs. Besides contamination with excessive or even banned pesticides, heavy metals (lead, arsenic, mercury, cadmium) and microbial products (*Aspergillus flavus*, Aflatoxin B1, Salmonella organisms), adulteration with synthetic therapeutic substances are one of the greatest risks using herbal products.⁹ In this respect, World Health Organization (WHO) offers needed standardizations and legislations concerning herbal drugs.¹⁰

CONCLUSION

It is concluded that adulteration of Chinese herbal remedies with conventional drugs is a potentially serious problem which causes high risk for consumer. Most of the people use these kinds of medications for the purpose of weight loss. Although marketing of such drugs is forbidden in Turkey, these products are still available via internet. Means of minimizing this risk should be found and implemented. International legislations and regulations concerning the marketing and producing traditional herbal products might be helpful to tackle this common public health issue.

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