

A 'natural' weight loss product containing sibutramine

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Introduction

For consumers who want to lose weight, using a product claiming to make that weight loss easier may be an attractive option. Herbal products are often perceived as safe because they are 'natural'. However, these products are not free of risks. Herbal products themselves can be a cause of adverse drug reactions^[1] but these products can also be adulterated with active pharmacological ingredients.²⁻⁴ A recent Dutch study determined whether herbal food supplements for weight loss on the Dutch market contained active pharmacological ingredients with weight loss properties. This study found that in 50 samples collected from August 2004 to May 2013, in 24 samples sibutramine, desmethyisibutramine (DMS), didesmethylsibutramine (DDMS), rimonabant, sildenafil, and/or the laxative phenolphthalein were identified. Some samples contained multiple active pharmacological ingredients. The presence of these ingredients was not stated on the label.^[4] In addition, several other studies have identified sibutramine and other active pharmacological ingredient in supposedly 'natural' products.^[2,5-8]

The Netherlands Pharmacovigilance Centre Lareb, located in 's Hertogenbosch in the Netherlands, collects and analyzes reports of adverse drug reactions (ADRs). By maintaining the reporting system for ADRs, Lareb monitors the safety of medicines and vaccines in the Netherlands. In addition to monitoring the safety of registered drugs and vaccines, healthcare professionals and the general public can also report non-registered herbal products and food supplements including vitamins. In the Netherlands, herbal products can obtain marketing authorization through the Dutch Medicines Evaluation Board (MEB) in the case that the same efficacy and safety data are available as for 'regular' drugs. A manufacturer can also apply for a marketing authorization as a 'traditional herbal drug' through the MEB, meaning that the efficacy of these products is assessed not by clinical testing but on the basis of a long history of use and experience. If an herbal product is not registered through the MEB, it falls under the Dutch Commodities Act. Information on the reported ADRs of these products under the Dutch Commodities Act is shared with the Netherlands Food and Consumer Product Safety Authority (NVWA).^[2,9]

At present, the database of Lareb contains 39 reports about un-registered slimming products, of which 9 were suspected of being adulterated with an illegal active pharmacological ingredient. In an additional 7 cases, high dosages of caffeine were added to weight loss products containing cactus, *Aurantii pericarpium* (bitter orange), *Yerba mate* (leaves), *Guarana* (Seeds), and *Kola nut* (seeds). For products where such a suspicion arises, Lareb requests the reporter (either a healthcare professional or consumer) to send a

sample of the product used. Lareb works in collaboration with the National Institute for Public Health and the Environment (Dutch abbreviation RIVM) and samples are sent to them for analysis. In case a product is found to be adulterated with an active pharmacological ingredient, Lareb also informs the Dutch Health Care Inspectorate, as counterfeit medicines and dietary supplements adulterated with drug substances on the Dutch market fall under their legal responsibility.

Case report

A 23-year-old woman had bought the herbal product 'Irem Naturel' as a slimming drug. The product was sold to her through a door-to-door sales method. On the first day of use she felt dizzy, had no appetite, a dry mouth, and could not fall asleep. On the second day of use she experienced dilated pupils, an increased heart rate, difficulty sleeping, confusion, aggressive behaviour, and sweating. On the third day she felt worse than on day two and she also suffered from disorientation. She stopped using the product but still had complaints for several days. After suffering from chills and an alternating hot/cold sensation, an increased heart rate, profuse sweating, and fainting on day five, she was taken by ambulance to the general practitioners post at the hospital. Here ibuprofen and antibiotics were given, as it was thought the complaints were due to an infection. After being released from hospital, the reporter mentioned that she slept for most of two days and then recovered. The patient is normally healthy; she exercised three days a week and did not use alcohol or drugs. Concomitant medication was an oral contraceptive pill. The patient had no known medical history.

The ingredients declared per capsule on the package of the product Irem Naturel were: Green tea 65 mg, citrus 100 mg, Guarana 50 mg, Red Chili Pepper 110 mg, Tragacanth gum 150 mg, and medical starch 25 mg.

Since the reporter herself was suspicious that the product might be adulterated by a non-declared registered drug and

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because she wanted to warn others of this product, she contacted the Netherlands Pharmacovigilance Centre Lareb. Lareb had received no earlier reports about this product, but asked the patient if she still had a sample of the product available for analysis. A sample of the product was then submitted for analysis to the RIVM.

Experimental

Materials

The sample consisted of 12 orange/grey capsules. The expiration date listed on the product was 03/01/2015 with Batch number 0219201401.

A sibutramine HCl reference standard was obtained from Sigma-Aldrich (Zwijndrecht, the Netherlands). Formic acid (p.a.), acetonitrile (p.a.), and ammonium hydroxide (p.a.) were obtained from Merck (Darmstadt, Germany). Water was deionized and filtered using a Millipak®200 0.22 µm filter from Millipore B.V. (Amsterdam, the Netherlands).

Instrumentation

Three capsules were emptied and their contents (ranging from 208 to 244 mg) were individually extracted with 100 mL of methanol in a volumetric flask. The methanol extracts of the samples were subsequently diluted 100-, 1000-, and 5000-fold in volumetric flasks in eluents containing 87% component A (5 mM ammonium formate, adjusted to pH 3.0 using formic acid) and 13% component B (0.1% formic acid in acetonitrile), before injection in the liquid chromatography-mass spectrometry (LC-MS).

The sibutramine reference standard was independently weighed two times and dissolved in methanol in a volumetric flask at 3.9262 mg/ 10 mL and 2.0015 mg/ 10 mL, and subsequently injected in four concentrations in duplicate, ranging from 0.1 to 0.8 mg/mL. Dilutions were made in volumetric flasks in eluents containing 87% component A and 13% B. Solutions were filtered

before use over a 0.2 µm filter (Spartan 30, Whatman GmbH, Dassel, Germany).

Chromatographic separation was performed using a Waters Acquity™ ultra-performance liquid chromatography (UPLC) system fitted with an HSS C18 column (150 mm x 2.1 mm i.d., 1.8 µm; Waters Chromatography B.V., Etten-Leur, the Netherlands). Detection of the analytes was carried out using a Waters Synapt™ G2 quadrupole time of flight (QTOF) mass spectrometer (Waters Chromatography B.V., Etten-Leur, the Netherlands) with a Z-spray electrospray ionization (ESI) source operating in the positive ion mode. MS^E data were acquired in the resolution mode (≥20,000 FWHM). Chromatographic and mass data were acquired and analyzed using Waters MassLynx v4.1 software. The presence of an analyte was confirmed by retention time, MS and MS/MS using a reference standard. Mass spectra and fragmentation patterns of sibutramine and benzyl-sibutramine were the same as reported before and major fragments matched the smaller fragments found by others.^[10,11] Quantification was performed using the [M + H]⁺ ion of sibutramine. Calibration samples were prepared in duplicate (Figure 1).

Results and discussion

The analysis showed that each capsule contained 18 mg sibutramine per capsule. There were also traces of the impurity benzyl-sibutramine detected. This is indicative for the use of inexpensive, substandard reagents used in the second synthesis step, where the nitrile is alkylated.^[12,13] Apparently, the isobutyl Grignard reagent is polluted with benzyl.^[10]

The product Irem Naturel is an example of a dietary supplement adulterated with a drug substance that is manufactured in Turkey and imported to other countries like the Netherlands. Dutch law forbids the marketing of such products, thus making Irem Naturel an illegal product. In the Netherlands it is sold by door-to-door sales methods, sales parties at home (reminiscent of Tupperware® parties) and through Facebook groups. A problem with the door-

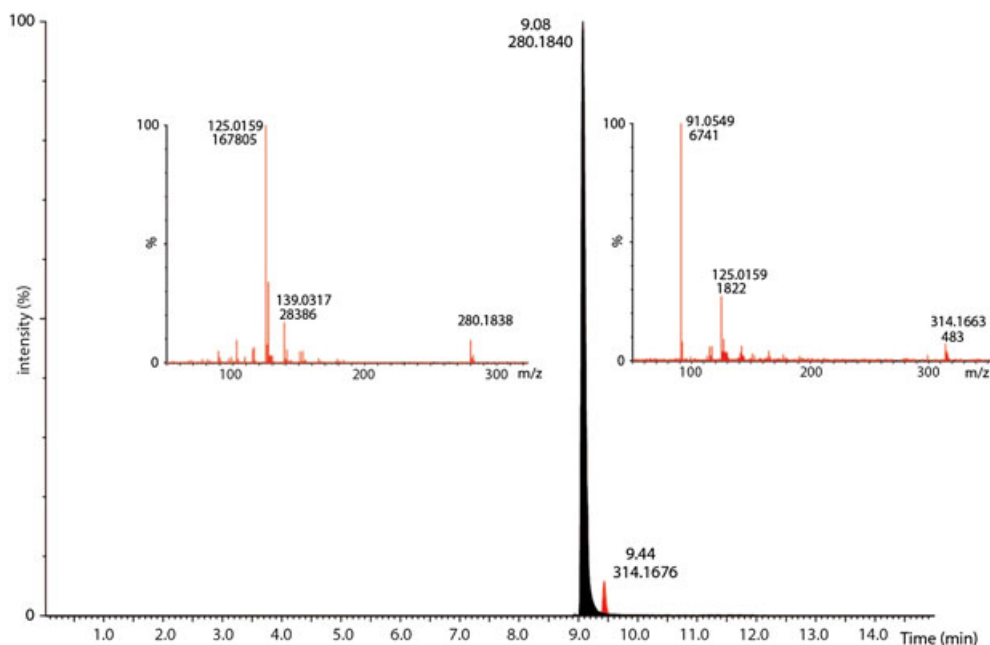


Figure 1. UPLC-QTOF MS-MS analysis of the product. Shown are the overlay of the extracted ion chromatograms of sibutramine at $m/z = 280.1832$ and benzyl-sibutramine at $m/z 314.1676$, with the MS₂ spectra of the two compounds as inserts.

to-door sales method and sales parties is that buyers and sellers know each other and that buyers who experience an adverse drug reaction might feel uncomfortable making this publically known. This was also the case with the consumer who reported to Lareb. For unlicensed products such as Irem Naturel, under-reporting of adverse drug reactions is likely to be significant, since users typically do not seek professional advice about their use of such products, or report if they experience adverse effects.^[1]

The illegal ingredient in this product is sibutramine, which is a 'serotonin-noradrenaline re-uptake inhibitor' (SNRI). In the EU, sibutramine was first authorized in January 1999. Sibutramine was available as capsules containing 10 mg or 15 mg sibutramine, under the trade name Reductil®, and as generic medicine.^[14] Because the long-term effects of sibutramine treatment on the rates of cardiovascular events and cardiovascular death among subjects at high cardiovascular risk had not been established, a large randomized controlled trial (SCOUT) was initiated. Subjects in this trial with preexisting cardiovascular conditions who were receiving long-term sibutramine treatment had an increased risk of nonfatal myocardial infarction and nonfatal stroke but not of cardiovascular death or death from any cause.^[15] In Europe, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency concluded on 6 August 2010 that the benefits of sibutramine-containing medicines did not outweigh their risks, and therefore recommended that the marketing authorizations for sibutramine-containing medicines be suspended across the EU.^[14]

Almost all the adverse drug reactions the patient in this case described are listed in the US product label for sibutramine and were seen in placebo-controlled studies, below the reactions that the patient experienced which were labelled or for which a similar ADR was labelled are listed; dizziness (incidence 7.0 %), anorexia (13.0 %), insomnia (10.7 %), dry mouth (17.2 %), sweating (2.5 %), tachycardia (2.6%), and flu syndrome (8.2%). As a psychiatric reaction, among others, emotional lability (1.3%) is listed. Also fever was seen with the use of sibutramine. The label also warns that because sibutramine can cause mydriasis, it should be used with caution in patients with narrow angle glaucoma.^[16]

The supplement the patient used also declared guarana (*Paullinia cupana*) as an ingredient on the packaging, which is a natural source of caffeine. The content of caffeine in this plant is high and can be up to 6% in the seeds.^[17] Caffeine, in high doses, can produce cardiovascular adverse effects, which include tachycardia. Acute caffeine poisoning resulting in atrial fibrillation after guarana extract overdose has been described.^[18] However, the declared dosage of guarana in this weight loss product is well within the limits for safe use. Because caffeine is the active ingredient in guarana, a maximum daily intake of caffeine for non-pregnant adults should be approximately 250 mg, which is the equivalent of 3 to 5 grams guarana.^[19] This product declared to contain 50 mg of guarana per tablet. Commonly found adulterants in herbal supplements intended for weight loss include sibutramine, ephedrine and amphetamine analogues, phenolphthalein, rimonabant, and dinitrophenol. In this study, the investigated samples were screened with an LC-MS library containing the compounds mentioned above as well as >1000 other active pharmaceutical ingredients. No caffeine was found in the samples. We did not specifically search for other guarana ingredients. In the analysis the method validation and quantification of the test samples was performed without the use of an internal standard.

According to the WHO-UMC system for standardized case causality assessment,^[20] the causality in this case is deemed

likely/probable. However, it is important to note that this is a case reported to the Netherlands Pharmacovigilance Centre by the patient herself and unfortunately no biological data (e.g. blood or urine) were available for further research. Also, unfortunately, the number of tablets the patient used per day is unknown. Since this is a reports from directly a consumer, the Netherlands Pharmacovigilance Centre Lareb did not have access to her medical records, thus the case remains medically unconfirmed. However, besides the received report there were multiple telephone conversations with the patient and she also provided her contact details to both the pharmacovigilance centre and the Dutch Healthcare Inspectorate. The reporter suspected that the product was adulterated but she did not know with which substance. To the best of our knowledge, there were no warnings on this product to be found online at the time of reporting. Based on the information she provided, the Netherlands Pharmacovigilance Centre Lareb has no doubt about the validity of the case. Consumer reports can be a valuable source on obtaining information on (adulterated) herbal products.^[21]

Conclusion

In differential diagnosis, it is important to be aware that dietary supplements or herbal drugs may be adulterated with active pharmacological ingredients like sibutramine. In this case the sibutramine content in the weight loss product was high enough to cause a pharmacological effect.

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