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CASE REPORT

The black market for anorectic agents: A case study of amfepramone

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Summary The black market for pharmaceuticals has grown in recent years, largely due to the easy trade of products over the Internet. This trend poses a potential risk to consumers' health, as it is not always possible to identify the origin of the products, which can be counterfeit. This study was designed to identify capsule components by full-scan mass spectrometry analyses coupled to liquid chromatography based on a single injection of the capsule material previously solubilized in methanol. The simultaneous analysis of other compounds that could be used as adulterants was performed in a fast chromatographic run based in a multi-step gradient, only 11 minutes were necessary to evaluated all the substance without isomeric co-elution. The mass spectrometer was set to operate switching the ionization mode: positive and negative, for FULL HRMS and all-ion fragmentation acquisition, simultaneously. By WhatsApp groups, the GloboNews reporting team purchased a box of amfepramone capsules from dealers of counterfeit controlled drugs. The contents of the capsules analyzed did not contain any traces of amfepramone or any anorectic agents. The result of this study suggest the need for greater and more effective control by competent authorities to avoid black market medicines and to combat drug smuggling and counterfeiting.

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Introduction

The black market for pharmaceuticals poses a potential risk to the consumer, as it is not always possible to identify the origin of the products, which can be stolen, of low quality, unregistered or forged [1,2].

According to reports of the International Chamber of Commerce (ICC), one-fifth of all branded medications in Brazil are counterfeit [3]. In Rio de Janeiro, the GloboNews reporting team uncovered the actions of dealers selling counterfeit controlled drugs. Through WhatsApp groups, boxes of controlled drugs can be obtained. In one of these sales groups, the GloboNews team purchased a box of a known brand-name appetite-suppressing drug, or an anorectic agent [4].

The drug was sold in an irregular way, without a medical indication, prescription or clinical follow-up. The laboratory responsible for manufacturing the original drug noticed that the product had not been manufactured since 2011 and that the last lots expired in 2014 [4].

Anorectic agents

Anorectic agents are dietary supplements or drugs that reduce appetite, leading to weight loss [5]. Since these drugs were first commercialized almost 50 years ago, Brazil leads in the consumption of anorectic agents, followed by the United States and Argentina. Compared to 1998, in 2005, there was a 500% increase in the consumption of these drugs [6].

In 2017, four appetite suppressant drugs were permitted in Brazil by Agência Nacional de Vigilância Sanitária (ANVISA): sibutramine, amfepramone, fenproporex and mazindol [7]. However, these drugs are allowed only in restricted cases and under medical prescription, anorectic drugs are restricted to patients with severe obesity and cannot be used by people who want to lose weight for aesthetic reasons [8].

These four recently approved drugs increase hormone levels and consequently activate noradrenergic, dopaminergic and serotoninergic receptors, increasing satiety [5]. However, it is possible to develop tolerance to appetite suppressants after continuous use. Notwithstanding, the abuse of these drugs, specially without clinical follow-up, can result in fatal pulmonary hypertension and heart valve damage [5,9,10].

Amfepramone

Also known as diethylpropion, amfepramone (2-(Diethylamino)-1-phenyl-1-propanone), was introduced to the worldwide market in 1958. Since 1980, the World Health Organization (WHO) has classified amfepramone as requiring high levels of international control. The abuse and illicit trafficking of amfepramone has been reported from nearly all regions of the world [11].

Along with other amphetamine-like drugs, amfepramone has central and peripheral stimulant properties and some important toxicological risks. Even when taken in therapeutic doses, it is possible to observe euphoria, irritability and delirium.

Moreover, in several South American countries, overuse of anorectic stimulants has led authorities to undertake additional educational and regulatory actions [6,7,11]. Statistics data from the Brazilian Doping Control Laboratory demonstrate a high prevalence of anorectic stimulants among Brazilian athletes, and amfepramone is one of the stimulants detected most regularly [12].

Therefore, the abuse of amfepramone and other anorectic agents in South America is likely underestimated, and the WHO declares that this substance constitutes a ''substantial'' risk to public health and recommends that informational and educational activities should be intensified to curb its overuse [11].

Liquid chromatography high-resolution mass spectrometry (LC-HRMS)

Chromatography coupled to mass spectrometry plays a key role in drug discovery [13]. Recently, improvements in HRMS instrumentation have increased accuracy and stability and enabled routine drug identification processes in laboratories [14]. The benchtop orbitrap analyzer, combined with a fast LC system, provides qualitative determinations based on the exact mass and retention time for targeted and untargeted analyses simultaneously [15].

This work sought to evaluate the capsules purchased by the GloboNews team using LC coupled to orbitrap detection.

Experimental

Chemicals and reagents

Ammonium formate (NH_4COOH), anhydrous sodium acetate and formaldehyde solution (37%) were obtained from Merck KGaA (Darmstadt, Germany). Acetic acid, formic acid (HCOOH) (96%) and methanol (MeOH) were obtained from Tedia (Fairfield, OH, USA). Ultrahigh purity water was obtained using a Milli-Q water dispensing system (Molshein, France).

Sample preparation

The drug samples were donated by the telecommunications company Globo News after purchase on the illegal market.

The drug capsules were opened and solubilized in 1 mL of MeOH under constant agitation for 5 min and centrifuged at 4,000 rpm for more 5 min. The collected supernatant was diluted in MeOH at a ratio of 1:100, dried under N_2 at 40 °C, and resuspended in a mixture of water and 2% acetic acid.

Analysis by LC-HRMS

The LC system consisted of an Accela MS pump and an Accela autosampler with a 50-μL sample loop (all from Thermo Products, Thermo, San Jose, CA, USA). A C18 column (50 mm × 2.1 mm, 1.9 μm, Thermo, San Jose, CA, USA) was used for the chromatographic separations. The column was maintained at 40 °C. The mobile phase consisted of water (A) and MeOH (B), which both contained 5 mM NH_4COOH/0.001% HCOOH. The gradient elution at a flow rate of 0.4 mL/min was: 95% A for 0.3 min, linear to 90% A in 0.5 min,

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