The undervalued issue of drug of abuse adulterants' toxicity: the Italian perspective

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ABSTRACT

The addition of active compounds to the principal drug at different stages of the supply chain is known as drug of abuse adulteration. The aim of this process is to modify or enhance the pharmacological activity of the drug in order to increase the dealers' profit. However, these mixtures may present unpredictable pharmacological properties, such as higher potency than the principal compound alone or new effects due to the drug interactions. For these reasons, inert and cheap diluents (as talc or sugars) have been replaced by active substances allowing to hide the low-quality of the principal drug (as procaine in cocaine or paracetamol in heroin). In recent years, several cases of intoxications (even with fatal consequences) have been reported in the United States, involving drugs with adulterants such as levamisole, phenacetine, aminopyrine, metamizole, diltiazem or xylazine. Evidences of ketamine in association with methylenedioxymethamphetamine (MDMA) or the synthetic cannabinoid methyl 3,3-dimethyl-2-(1-(pent-4-en-1-yl)-1H-indazole-3-carboxamido) butanoate (MDMB-4en-PINACA) with low Δ9-tetrahydrocannabinol (Δ9-THC) content have been reported in Europe. An Italian case of heroin and xylazine was reported in 2023, and confirmatory analyses suggested that xylazine played a role in determining the death, given the low level of morphine detected. Toxicology laboratories are required to perform a comprehensive examination of adulterants and their market trends to define drug consumption patterns. Drug adulterants represent an ever-new challenge to toxicology laboratories which should be prepared to detect even unsuspected molecules in intoxication or death cases.

Key words: *drug interactions, xylazine, drug adulteration*

INTRODUCTION

The drug of abuse adulteration is the common practice of adding active compounds to the principal drug at different stages of the supply chain to enhance or modify the pharmacological activity with the aim to increase the drug dealers' profit in different ways. These mixtures may present unexpected pharmacological properties such as incredibly high potency or new effects due to the interactions, justifying a higher price on the market. However, not only the recreational effects are influenced by the adulterants, since these substances present a specific toxicological profile which could be enhanced by those of the principal drugs, resulting in unexpected toxicity due to pharmacological interaction (1,2). Thence, the observed adverse effects might be related to the adulterants themselves or to the combination (3).

Over the years, the quality of drugs proposed on the illegal market has been changing continuously. To this concern, inert and cheap diluents such as talc or sugars, have been replaced by active substances which allow to mask the low-quality of the principal drug, like procaine in cocaine or paracetamol in heroin (4).

The emergence of New Psychoactive Substances (NPS) has further complicated the scenario since these compounds are often added to the common drug of abuse, causing an increase in misinterpreted fatal and non-fatal intoxications all over the world (5,6). Due to their controversial legal status, these molecules are easily distributed through specialized websites or internet

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at a cheaper price than the common drug of abuse due to the reduced manufacturing costs.

Social, economic and political factors impact the drug market, influencing the availability of certain substances or modifying the normal distribution routes. Indeed, the SARS-CoV2 pandemic restrictions represent the most recent evidence of the role played by specific restrictions adopted by single Countries (7). As a consequence, the shortage of raw materials for natural or semi-synthetic drugs of abuse, such as heroin or cocaine, has pushed drug dealers to propose to the drug users new alternatives that have been established over the years. This phenomenon involves also diverted pharmaceutical drugs with psychotropic or narcotic effects. Recently, the veterinary sedative xylazine has appeared on the US illicit market in combination with fentanyl, its analogues or heroin (7). The unintentional exposure to this molecule was revealed in 9% of opioid-related overdose cases that occurred in Philadelphia between 2021 and 2022, (7) while higher rate of fatalities was observed in other US countries, such as Delaware which reported about 16% of positivity to xylazine. Lately, xylazine has arrived in Europe where it was reported for the first time in the UK as opioid adulterant. Besides the new adulterants, more established substances have never disappeared from the illicit drug manufacturing process, causing an ever-increasing number of related pathologies such as cardiovascular events due to levamisole-adulterated cocaine.

For these reasons, a comprehensive view on adulterants and their market trends plays a crucial role for toxicology laboratories to define drug consumption patterns and to trace intoxication cases.

ADULTERANTS

The American scenario

The US State Department has been working with the Colombo Plan, (an independent intergovernmental organization) for more than 30 years, to obtain information on the characteristics of overdose epidemics related to opioids and other illicit drugs and to identify toxic adulterants used in the production of illicit drugs in the USA (8).

Before 2000s, diluents such as mannitol or lactose were added to increase profits by decreasing the amount of product, with little side effects on consumers. Since 2010, these inactive compounds have been replaced by pharmacologically active substances, such as levamisole, phenacetin, aminopyrine, metamizole (or dipyrone), diltiazem or xylazine, which are the cause of many intoxications, even with fatal outcomes. Most of the detected toxic adulterants have been associated with adverse effects, including blood disorders (neutropenia, anemia), multifocal inflammatory leukoencephalopathy, hemolytic uremic syndrome, renal failure, liver toxicity, multiple malignancies, infectious diseases, respiratory depression, life-threatening cardiac arrhythmias and cardiac arrest (9). Recently, many cases of overdose caused by the mixture of fentanyl and new benzodiazepines (as etizolam) were reported and this phenomenon is known as “benzo dope”. The effects of this combination are a prolonged loss of consciousness and a severe respiratory depression (10). Therefore, the danger is not only represented by the toxicity of these adulterants, but also by the unpredictability and unknown synergistic reactions with other substances, increasing the risk of adverse health consequences, including death.

The European scenario

In the last years, the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) highlighted the presence of adulterants in drugs of abuse in Europe (11). Specifically, there has been evidence of widespread consumption of ketamine alone or in association with methylenedioxymethamphetamine (MDMA). Other adulterants for MDMA are synthetic cathinones. Many European countries reported alerts for cannabis products with low Δ9-tetrahydrocannabinol (Δ9-THC) content, which resulted in being adulterated with the synthetic cannabinoid methyl 3,3-dimethyl-2-(1-(pent-4-en-1-yl)-1H-indazole-3-carboxamido) butanoate (MDMB-4en-PINACA) (12). In 2022-2023, 54 cases of deaths tested positive for nitazenes in the UK. These substances are very potent synthetic opioids used as adulterants for other opioids, benzodiazepines and cannabis products (13).

The Italian scenario

In Italy, since 2009, the Anti-Drug Policies Department of the Italian Presidency of the Ministers Council has established the National Early Warning System, [Sistema Nazionale di Allerta Precoce (SNAP)], receiving a European directive (14). As part of an European network coordinated by the European Monitoring Centre on Drug and Drug Addiction, the SNAP system focuses on the early detection of new NPS and new trends in the illicit market on the Italian territory. Furthermore, all the collected data on NPS are rapidly shared through the capillary network of the collaborative centers as I, II or III grade alerts, depending on the risk assessment of each case. In 2023, two distinct alerts were issued on the risk related to drug adulterants involved in intoxication cases reported to the SNAP.

In summer 2023, the EMCDDA advised the National Center on Addiction and Doping of the National Institute of Health, coordinator of the SNAP, on a suspected fatal intoxication series involving drug users in a short period in the same area of Sardinia. Hence, the available postmortem samples were promptly requested by the prosecutor to further investigate the cause of death, reported as drug-related fatal intoxication for all the cases. The post-mortem blood and urine samples were extracted according to the laboratory procedure and analyzed by a validated Liquid Chromatography-High Resolution Mass Spectrometry (LC-HRMS/MS) screening method which allows to sensitively detect more than 1000 psychotropic drugs. The analyses revealed the presence of morphine and its metabolites as biomarkers of heroin consumption

together with xylazine. The quantitative confirmatory analyses performed in Gas-Chromatography-Mass Spectometry (GC-MS) and LC-HRMS/MS suggested that xylazine played a role in the determination of the death, since morphine was quantified at a relatively low amount (total morphine in blood 235.7 ng/mL). As a consequence, a III grade alert was immediately issued to advise the presence of this new harm on the Italian territory. Soon after, the Service for Drug Addiction (SerD) based in Campania region, in the south of Italy, contacted the National Centre on Addiction and Doping to report an alleged xylazine non-fatal intoxication. A polydrug consumer in opioid substitution therapy in the SerD presented ulcers on both the legs, similar to those provoked by chronic consumption of xylazine. However, the LC-HRMS/MS analysis of urine and hair samples disclosed the undeclared consumption of cocaine adulterated with levamisole. As reported in the literature, the chronic exposure to levamisole may cause peripheral vasculitis exerting ulcers. In 2016, two fatal cases were reported in the literature due to cocaine adultered with levamisole (15). Histological findings corroborated the correlation between the high concentration of levamisole quantified in post-mortem biological matrices and pulmonary lymphocytic vasculitis.

The two cases reported to SNAP highlight the importance of sharing information to better understand not only new trends in drug adulteration but also unexpected symptoms/effects, together with the ability of laboratories to detect not only classic drugs and NPS but also adulterants.

CONCLUSION

Drug adulteration is a fluctuating phenomenon which follows the illicit market trends, proposing a wide range of active principles to enhance the recreational effects of the principal drug and obtain a higher profit. Similarly to the NPS phenomenon, drug adulterants pose an ever-new challenge to the toxicology laboratory which should be prepared to detect even unsuspected molecules. To this concern, the development of comprehensive analytical methods to detect a wide range of molecules in the biological matrices could not be sufficient without a strong interlaboratory collaboration based on the mutual exchange of information and analytical support.

CONFLICT OF INTEREST

None

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