Case Report

Euromediterranean Biomedical Journal
for young doctors
(formerly: Capsula Eburnea)

ASSESSMENT OF TOXICITY DUE TO INTRAVENOUS ADMINISTRATION OF HEROIN CUT WITH CAFFEINE IN A CHRONIC CITALOPRAM CONSUMER.

Nunziata Barbera, Andrea Bosco, Francesca Indorato, Guido Romano

SUMMARY

This article presents the case of a 26 year old male heroin addict and chronic user of high doses of citalopram, who was found dead at his home. Toxicological analysis showed that the young man was in a state of chronic citalopram intoxication. The low opioid concentration detected excluded heroin overdose as the cause of death.

The heroin used by the man was characterized by a low percentage of opiates (heroin 0.1%, acetylcodeine 0.8%; 6-MAM 1.19%, codeine 0.2%) and a high percentage of cutting substances (caffeine 38%, acetaminophen 29%).

The pathogenetic mechanism underlying the man's death was reconstructed through the integrated evaluation of analytical and pathological data together with consideration of the toxic effects of intravenous injection of heroin cut with a significant amount of caffeine (although non-lethal) in the presence of high citalopram concentrations.

Introduction

The term ***overdose*** denotes acute intoxication from drugs. It is one of the most dangerous situations in which a drug addict may find him/herself; it can comprise vital functions and lead to death.

As regards the forensic diagnosis, heroin-related deaths are usually a consequence of acute intoxication relative to tolerance, a definition that refers to those cases where the consumed dose is relatively superior to the degree of tolerance reached by the subject. However, the cause of death is in many cases traceable to various factors. For example, a particularly low state of tolerance of the subject, the presence of particular pathological states or contingent situations of debilitation of the organism may assume considerable importance. Furthermore, the synergic effect produced by the previous or concomitant assumption of other drugs, such as alcohol or psychotropic drugs, can sometimes be determinant.

Here we report a a singular case of death following intravenous consumption of heroin cut with a high percentage of caffeine. The peculiarity of the case arises from the fact that the man involved was, as well as a heroin addict, also a chronic consumer of high doses of citalopram.

Case description

A 26 year-old man was found dead at his home. A syringe with recent traces of blood and two spoons (used to melt the dose of the drug) were found next to the body.

It emerged from the police's initial investigations that the previous day the young man had purchased three doses of heroin. An inspection of the dealer's home (the dealer who

Address of the authors
Department "G. F. Ingrassia" – Section of Legal Medicine – Laboratory of Forensic Toxicology - University of Catania

***Send correspondence to**: Nunziata Barbera, toxicologyct@hotmail.com*

***Received**: November 20th, 2012 — **Revised**: February 12th, 2013 — **Accepted**: March 27th, 2013*

the previous day had sold the three doses to the young man) ensued and two "doses" of heroin, weighing about 250 mg each, were confiscated.
The autopsy allowed for the exclusion of traumatic injuries caused by third parties, as well as macroscopically detectable pathological events. Instead, a diffuse polivisceral congestion with pulmonary edema was found.
Histopathological investigations confirmed the picture observed at autopsy, detecting marked congestion of the brain and cerebellum associated to subarachnoid hemorrhagic microfoci; diffuse intra-alveolar pulmonary edema with exudation of abundant emosiderophage histiocytes (due to static circle) and extended subpleural areas of intra-alveolar hemorrhage alternated with emphysema. The heart displayed microscopic foci of coagulative necrosis.

Results

The toxicological analyses performed on viscera and body fluids revealed the presence of low concentrations of morphine and high concentrations of caffeine and citalopram (Table 1). Neither alcohol nor other drugs were found in the blood sample.
High concentrations of opiates (codeine 0.2 ng/mg; morphine 4.7 ng/mg; 6-MAM 1.26 ng/mg) and citalopram (12.3 ng/mg) were found in hair matrices.
A low percentage of opiates (heroin 0.1%; acetilcodeine 0.8%; 6-MAM 1.19%; codeine 0.2%) and a high percentage of cutting substances (caffeine 38%; paracetamol 29%) were found in both heroin "doses" sequestered at the home of the drug dealer.
Analysis of the spoons and the syringe used by the young man showed the presence of residues of a substance with the same composition of that seized from the dealer (low percentage of opiates and high percentage of cutting substances: caffeine and paracetamol).

Discussion

The interesting feature of the presented case is that the young man was, as well as a heroin addict, also a chronic consumer of high doses of citalopram.
In particular, analytical, circumstantial and anamnestic data clearly bear testimony to the fact that the man was a habitual consumer of heroin and that before death he repeatedly took intravenous doses of heroin. The presence of 6-MAM in the brain, particularly in the lung and in the blood, indicated that death occurred shortly after the last dose (1).
However, considering that the man was a chronic heroin addict, the concentrations of morphine, 6-MAM and codeine found in his body were too modest to allow for a correlation between death and a lethal overdose of opiates. In fact analysis performed on the drug seized from the dealer highlighted the presence of a low percentage of opiates (heroin 0.1%; acetilcodeine 0.8%; 6-MAM 1.19%; codeine 0.2%) so that each single "dose" of 250 mg could contain, at most, an overall quantity of opiates of about 5.7 mg. This quantity was insufficient to cause death by overdose. Further analyses showed a particularly high percentage of the cutting substances: caffeine 38% and paracetamol 29%.

Substances	Blood	Vitreous humor	Brain	Lung	Liver	Kidney	Gastric contents	Bile	Urine
Morphine	110	328	194	219	401	537	228	18,935	15,362
6-MAM	0.93	26.8	7.7	10.7	n.d.	n.d.	95.4	n.d.	n.d.
Codeine	25	31	29	44	33	44	28	67	431
Citalopram	758	1,129	1,507	n.a.	n.a.	n.a.	396	n.a.	7,239
Caffeine	2,998	1,550	2,533	n.a.	n.a.	n.a.	5,903	n.a.	1,894

[a] *n.d.: not detected; n.a.: not analyzed*

Table 1: Opiates, caffeine and citalopram concentration found in viscera (ng/g) and biological liquids (ng/ml).

Moreover, elevated citalopram concentrations both in the blood (0.758 mcg/g) and in the other examined samples were found (Table 1). The integrated evaluation of all the data in our possession indicated that the concentrations of citalopram found in the man, even if high, were linkable more to a condition of chronic abuse than to a state of acute intoxication. This statement was supported by the presence of high concentrations of citalopram in the urine and hair matrices.

On the basis of the results obtained, the man's death could not be related to heroin overdose nor to fatal acute citalopram intoxication. Therefore, the toxic action caused by the cutting substances (specifically the caffeine present in unusually high percentages) and the concomitant condition of chronic citalopram intoxication played a key role in the pathogenic mechanism of death.

It is well known that citalopram is an antidepressant belonging to the pharmacological class of selective serotonin reuptake inhibitors (SSRI). It is indistinguishable from its isomer escitalopram through common analytical methods. Therapeutic concentrations are generally within a range of between 20 and 200 ng/ml (2) while the acute lethal range is above 0.5 mcg/ml (2); according to the International Association of Forensic Toxicologists (TIAFT), toxic concentrations are instead between 400 and 900 ng/ml (3).

Among the toxic effects of over-dosage of citalopram, those affecting the cardiovascular system are the most fearsome, both in acute and in chronic administration. These are represented by multiple alterations of the cardiac rhythm, which go from a slight bradycardia, to ventricular and supraventricular tachyarrhythmia, up to ventricular fibrillation and cardiac arrest (4).

The alteration of the cardiac rhythm is considered to be at the base of the pathogenic mechanism underlying deaths due to acute intoxication (4). In particular, citalopram, in daily doses superior to 40 mg/die (5), induces a prolongation of the ventricular repolarization phase (lengthening of the Q-T tract) detectable through electrocardiography (4-6). Experimental studies seem to indicate that citalopram, blocking potassium channels, prevents the output current from the cell with a consequent increase of the repolarization times (6). The lengthening of the Q-T tract can lead to depolarizing currents that, if they reach an adequate width, can trigger new depolarizations, both single or repetitive, causing a predisposition to severe rhythm disorders which if not treated, can rapidly evolve into fatal arrhythmias – such as ventricular fibrillation – and therefore to cardiac arrest (6).

In the process that leads to the onset of lethal acute poisoning, much depends not only on the hematic concentration reached, but also on the eventual concomitant consumption of other substances.

In this case, considering the cardiotoxic effects of chronic citalopram abuse, it was fundamental to evaluate the concomitant consumption of caffeine, especially because it was found in a high percentage as a "cutting substance" (115 mg/dose).

Caffeine is a 1,3,7-trimetilxanthine. The toxicity of methylxanthines is expressed on multiple organs and systems, particularly in the central nervous system and the cardiovascular system (7). The methylated xanthines cause an increase in heart rate and, in toxic states, can cause different types of arrhythmias (8). Particularly, in patients with underlying cardiac disease, a sinus tachycardia can degenerate into a more severe rhythm disturbance (9). Such arrhythmias, if prolonged, could be fatal (8).

Additional side effects of methylxanthines are hypokalemia (2) and, at toxic concentrations, metabolic acidosis (8). Both metabolic acidosis and hypokalemia can significantly increase the risk of cardiac arrhythmias (8). The fatal poisoning cases described in literature concern only suicidal or accidental cases of oral caffeine intake (9). In such cases, the toxic effects of caffeine occurred at serum concentrations greater than 15 mcg/ml (2) and only concentrations above 80 mcg/ml were associated with lethal cases (2).

Caffeine is not used in therapy by intravenous injection; it is taken through this route only together with heroin, in which it is generally present – in relatively modest percentages – as a "cutting substance". So, in the case reported, intravenous injection of such a high dose of caffeine has played a key role in the pathogenic mechanism of death, especially considering the high degree of bioavailability due to the rapid

intravenous administration. As well known in clinical practice, the rapid intravenous administration of methylxanthines may cause death from cardiac arrest even at therapeutic doses and without prodromal symptoms (10).

In the case reported, intravenous injection, and therefore the sudden blood peak of caffeine, even if not in a lethal amount, caused an increase of catecholamine which resulted in a rise in heart rhythm and in myocardial oxygen consumption. The concomitant state of chronic citalopram intoxication determined the conditions favorable to the onset of a lethal arrhythmogenic disorder and/or myocardial conduction abnormality (e.g., torsades de pointes, ventricular tachycardia, ventricular fibrillation) leading to circulatory arrest. The anatomopathological data support the pathogenic mechanism showing that the man's death occurred after a long and agonizing period characterized by severe acute heart failure with stasis of the circulation.

Therefore, toxicological analysis has allowed us to reveal the real cause of death, emphasizing the fundamental role played by cutting substances in the pathogenic mechanism of death.

References

1.Barbera N, Spadaro G, Santangelo F, Romano G. La valutazione del dato tossicologico-forense nella diagnosi di morte da eroina. Bollettino della Società Medico-Chirurgica di Catania 2001; LXX:28-39

2.Moffat AC, Osselton MD, Widdop B. Clarke's analysis of drugs and poisons. Pharmaceutical Press, London, 2004.

3.Dragsholt C, Worm K, Simonsen KW, Kringsholm B. Therapeutic, toxic, and lethal concentrations of citalopram. Poster session 3 presented at: SOFT – TIAFT 1998; October 8, 1998; Albuquerque, New Mexico, USA.

4.Tarabar AF, Hoffman RS, Nelson L. Citalopram overdose: late presentation of torsades de pointes (TdP) with cardiac arrest. J Med Toxicol 2008; 4:101-105.

5.FDA Drug Safety Communication: Revised recommendations for Celexa (citalopram hydrobromide) related to a potential risk of abnormal heart rhythms with high doses. The latest update: 28.03.2012. Available from: http://www.fda.gov/Drugs/DrugSafety/ucm297391.htm

6.Lee HM, Hahn SJ, Choi BH Open channel block of Kv1.5 currents by citalopram. ActaPharmacol Sin 2010; 31:429-435.

7.Boison D. Methylxanthines, seizures, and excitotoxicity. Handb Exp Pharmacol 2011; 200:251-266.

8.Fauci A, Braunwald E, Kasper DL, Hauser SL, Longo DL, Jameson JL, Loscalzo J. Harrison's Principles of Internal Medicine. McGraw-Hill, New York, 2008.

9.Goldfrank LR, Flomenbaum N,Hoffman RS. Goldfrank's toxicologic emergencies. McGraw Hill, New York, 2006.

10.RudolphT, Knudsen K. A case of fatal caffeine poisoning. Acta Anaesthesiol Scand 2010; 54:521-523