Study on Forms of Intoxication with Cocaine and Evolutionary Aspects

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Cocaine is an alkaloid obtained from the leaves of the coca plant, Erythroxylum coca. Cocaine sulfate, a brown paste, is obtained from coca leaves and from this, cocaine hydrochloride, a white substance, soluble in water and with a bitter taste that may be in the form of white crystals or powder. From cocaine hydrochloride crack is obtained by heating, a more purified form and with greater power of intoxication and addiction. Once in the organism, cocaine behaves like an indirect sympathomimetic amine and produces a blockade of the presynaptic reuptake of dopamine, adrenaline, noradrenaline and serotonin, thus increasing their levels. At the cardiovascular level cocaine is responsible for malignant arrhythmias, sometimes responsible for sudden death. Other symptoms that can occur are aortic dissection, arterial hypertension and coronary vasoconstriction able to trigger an acute myocardial infarction. The authors present a case of sudden cardiac death due to cocaine intoxication in a young male without any cardiac risk factors. The autopsy, together with the results of the complementary tests, indicate that the most probable death mechanism has been a cardiogenic shock secondary to extensive myocardial necrosis due to cocaine intoxication.

Keywords: cocaine, alkaloid, intoxication, cardiogenic shock, death, autopsy

Narcotics are defined as substances (solid, liquid or gaseous) of natural origin (vegetal, animal, mineral) or obtained by synthesis/semi-synthesis, characterized by a high potential to induce dependence and tolerance.

Drug dependence is the set of physiological, behavioral and cognitive phenomena related to the consumption of a substance, consumption that has a priority aspect despite the negative effects it causes need for a substantial increase in the amount of the substance to cause poisoning or the desired effect. Drug dependence also affects women and men with penetrability in all social environments [1, 2].

Cocaine is a natural alkaloid, isolated from the leaves of the plant Erythroxylum coca originating from South America. Cocaine is a psychostimulant sympathomimetic drug and was the first local anesthetic discovered. It is a benzoic ester and contains a nitrogenous base with the same structure as the local anesthetics that are currently synthesized [1, 2].

By chemically treating the coca leaves, coca paste is formed. According to the process applied to the coca paste, two chemical forms of cocaine can be obtained. When treated with hydrochloric acid it becomes a cocaine salt, the cocaine hydrochloride, also referred to as cocaine powder. Cocaine powder is water soluble, so it can be dissolved and injected easily. It is also liposoluble, which allows its absorption by the nasal mucosa (snorting) [3]. If cocaine hydrochloride loses the chloride ion, cocaine-base is obtained. Cocaine base is liposoluble, but little water soluble, volatile at low temperature and very suitable for smoke. Cocaine base is usually obtained by heating an aqueous solution of ammonia or sodium bicarbonate with cocaine hydrochloride until the cocaine base aggregates float in the liquid. The aggregates are extracted and dried, resulting in a smokable product that is often called crack [4]. Its purity is generally higher than that of cocaine hydrochloride, but crack may contain impurities and additives from cocaine hydrochloride and alkali remains used in the processing. It is, therefore, different from the freebase up to 95% pure and usually obtained by boiling cocaine hydrochloride and alkali with a solvent such as ether, a process that eliminates almost all additives and impurities [4, 5]. Despite this distinction, the term crack is used to refer to any type of cocaine-base or free base.

Both the chemical presentation and route of administration will determine the pharmacokinetic properties of cocaine. Cocaine powder is usually consumed intranasally (snorted), it takes minutes to produce the euphoria and reaches the peak plasmatic concentration within 30-40 min. Its maximum bioavailability is 40% and the duration of the effect is relatively long (60 min). Its consumption by injection or smoking is rare, although in both ways it would reach the brain faster but the duration of its effect would be shorter [6].

The cocaine-base or crack is consumed mostly via the pulmonary route, reaching the brain in a few seconds and producing an intense euphoria. The duration of the effect is shorter, approximately 30-45 min [4-6]. These characteristics give it great addictive power, higher than that of cocaine powder.

In general, cocaine has a short half-life (from 30 min to 1.5 h, depending on the type of consumption), and concentrates mainly in the brain, spleen, kidneys and lungs. It is metabolized in the liver producing some inactive metabolites (benzoylecgonine (BE) (45%), methyl-sterecgonin (45%), ecgonine) and an active metabolite (norcocaine). These metabolites are important in forensic medicine in establishing death cause since they can be detected in postmortem toxicological analyzes. They can be found in the urine 3-4 h after consumption, and although the clearance of cocaine via the kidney is rapid, it can be stored in adipose tissue a couple of hours (especially BE). However, it can be detected in other tissues, such as the brain, vitreous humor and liver up to 8 hours after its initial consumption. The different metabolites that are detected can also indicate the type of consumption chronic or acute [7-10].

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Scientific literature [4-7] has been focusing for a long time, on the relative connection between disadvantaged social categories and their susceptibility towards criminality, rather than focusing on the public health problems that are, usually more important. This kind of attitude has been promoting traffic and smuggling but also the tightening the law towards controlling distribution and not decreasing the production.

Cocaine consumption can lead to cardiac failure, hallucinations, stroke and other nervous system problems. The effects that can has on human body can be classified by how permanent they are: short time effects are anxiety, petulance, vascular constriction, fever, hypertension, and increased cardiac rhythm; long term effects are paranoia, aggressivity, nasal mucosa ulcerations and chronic depression, etc. Cocaine has a direct activity on the accumbens nucleus, one of the pleasure cores of the human brain. Is known that sex, food, alcohol and other pleasing sensations can amplify the accumbens activity, there by stimulating an increased dopamine release in synaptic bonds and thereby, a continuous excitation on the targeted neurons with constant euphoria.

Immediately after taking a dose of cocaine, the consumer will feel a powerful energy, increased attention and vigilance. Every visual, acoustic and tactile sensation is boosted, and hunger and tiredness disappear. Depending on the manner of administration, the drug effect can last up to 30 min. When smoked, cocaine can produce more intense effects that can last a shorter period compared to inhalation effects. When the drug is combined with alcohol consumption, the resulting substances are even more neurotoxic.

Sniffing cocaine, will produce in a very short time, vasoconstriction, hypertension and accelerated heartbeats and fever. These symptoms can be accompanied by vertigo, muscle spasm and acoustic hallucinations. Long term consumption can lead to cardiac infarction or stroke. Even for survivors, there are irreversible damages such as: nasal mucosa alterations, constant haemorrhage and complete loss of the smell. Drug ingestion can lead to sever alteration of the gastro-intestinal tract with severe abdominal pain, nausea and even infarction of the bowels.

Ingestion of Cocaine associated with levamisole may produce agranulocytosis, a blood disease which strongly decreases the number of white blood cells up to the inhibition of the body's ability to fight with infections. On the illegal drug markets, counterfeit produces are frequently distributed, by mixing cocaine with other naturally occurring or semisynthetic substances with narcotic effect, more easily procured, but with a very high toxicity. In this way, cocaine sold by dealers on the street is diluted with different substances, as: corn starch, sugar, and, rarely, with bicarbonate, talcum or caffeine. Often, illegal produces may contain procaine, lidocaine or other local anaesthetics, which simulate some effects, among which is tongue anaesthesia. Also, counterfeit cocaine is mixed with other drugs, heroine or amphetamines.

This paper presents a sudden death case which was provoked by cocaine overdose at a young person, without cardiac risk factors. Autopsy together with results of the results of complementary investigations, by means of physio-chemical and microbiological methods, indicates that the most likely mechanism of death was cardiogenic shock secondary to extensive myocardial necrosis due to cocaine intoxication on a background of ethanol consumption.

Experimental part

Material and methods

As It is well known, cocaine (benzyl-methyl ecgonine) is a natural crystalline tropane-type alkaloid, which inhibits dopamine, noradrenaline and serotonin. Also, it blocks transmission of the nervous impulse to the neuronal synapses by raising the receptor sensitivity threshold and increases sympathicotonia, which induces a state of euphoria and addiction. Cocaine chemical formula is C17H21NO4 which corresponds to the structure in figure 1. IUPAC is methyl(1R,2R,3S,5S)-3-(benzoyloxy)-8-methyl-8- azabicyclo octane-2-carbxylat, with a molar mass 303.36 g/mol, melting point 98°C and boiling point 187°C.

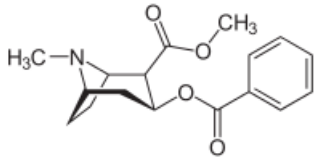

Fig. 1. Cocaine chemical formula

In this study, a young male died at short time after cocaine abuse, and during the autopsy samples were taken, such as blood, urine, vitreous humour and gastric contents, which was analysed by complementary physico-chemical and microbiological methods [11-13], and following the autopsy, there were changes in brain, lungs and heart levels, that were observed.

The experimental procedures were carried out in accordance with the mandatory principles of the Ethical Committee of the Grigore T. Popa University of Medicine and Pharmacy Iasi [14-16].

Results and discussions

The authors describe the case of a 34-years-old male without any cardiac risk factors or personal history. At a party, he consumed drugs and at one moment he went to the private room. Not returning for a half an hour, another participant to the party went looking for him. He declared having heard him breathing with difficulty so he took him out of the private room and laid him on the bed. A few minutes later, the young man died on site.

The external examination of the body revealed the corpse of a young male adult, tattooed, with low weight, an important erythema of the nasal mucosa, cervical-cephalic congestion and no signs of trauma.

The internal examination, after opening the cranial cavity, revealed a congested and edematous brain, with effacement of the grooves and accumulation of fluid without any hemorrhagic areas or contusion.

Examination of thoracic organs revealed congested and edematous lungs, with respective weights of 690 g for the right and 585 g for the left. After cutting the pulmonary parenchyma, a large amount of bloody fluid mixed with dark foam and air bubbles flowed, with the cut area showing patches of reddish color on its surface. When dissecting the bronchial tree, remains of the same substance were seen.

Cardiomegaly (565 g), with hypertrophy of the left ventricle and hemorrhagic lesions in the right atrium was also discovered. Dissection of the coronary arteries revealed no significant lesions, just mild non-obstructive atheromatous plaques in the left anterior descending artery.

Samples of blood, urine, vitreous humor and gastric contents were taken for toxicological analysis. The presence of cocaine and its blood metabolites was detected together with ethylic alcohol. Myocardial enzymes displayed high values: troponin I (cTnI) 20.19 ng/mL and creatine kinase-muscle brain (CK-MB): 9.8 ng/mL.

The autopsy, together with the results of the complementary tests, indicate that the most probable death mechanism has been a cardiogenic shock secondary to extensive myocardial necrosis due to cocaine intoxication.

Once in the organism, cocaine behaves as an indirect sympathomimetic amine and produces a blockade of the presynaptic reuptake of dopamine, adrenaline, noradrenaline and serotonin, thus increasing their levels.

After its absorption, cocaine is rapidly metabolized in the liver by means of cholinesterase, plasma pseudo-cholinesterase and non-enzymatic hydrolysis, giving rise to water-soluble products such as benzoylecgonine and ecgonine methyl ester, which are eliminated by the kidneys along with a small percentage of free cocaine, which can be identified in urine [17].

Any dose is potentially toxic, with deaths even after a first use. In general, it is difficult to predict which exposure will be toxic, due to the variability in the degree of purity and the different individual tolerance of consumers. Low plasma levels of cholinesterase are related to the presence of toxic reactions even at low doses, as the organism cannot hydrolyze cocaine rapidly. The combined use of cocaine and alcohol gives rise to a metabolite, cocaethylene, which prolongs the euphoria, produces greater myocardial depression and increases the half-life by 2.5 times compared to cocaine alone thus leading to late clinical manifestations [18-20].

There are tables of toxic and lethal concentrations of different xenobiotics for the toxicological diagnosis. Repetto et al. [21] consider that a fatal cocaine intoxication occurs when cocaine blood levels exceed 1 mg/L and benzoidecgonin urinary concentration exceeds 35 mg/L. Musshoff et al. [22] on the other hand, consider cocaine lethal even at lower doses like 0.5-1 mg/L of cocaine in blood.

The excess of biogenic amines produced by cocaine is responsible for the sympathomimetic toxic syndrome with tachycardia, diaphoresis, psychomotor agitation, altered mental status, mydriasis and hyperthermia.

In the central nervous system, cocaine can cause both ischemic and hemorrhagic vascular accidents and can lead to a series of seizures and intracranial hemorrhages without a predisposing anatomical substrate [6], as well as psychiatric disorders. Ischemic strokes are explained by the arteriosclerotic and thrombogenic action of cocaine because the damage to the endothelium of the cerebral arteries.

In the pulmonary sphere, pneumothorax, pneumomediastinum, asthma attacks, non-cardiogenic pulmonary edema, diffuse alveolar hemorrhage, interstitial pneumonitis, bronchiolitis obliterans, and acute pulmonary infiltrates associated with crack lung may occur [8, 23, 24].

At the cardiovascular level, cocaine can produce malignant arrhythmias such as atrial fibrillation, ventricular and supraventricular tachycardia, torsades de pointes, responsible for sudden death in many cases. Other symptoms that can occur are aortic dissection, arterial hypertension and coronary vasoconstriction able to produce acute myocardial infarction (AMI) [25]. It has been observed that acute myocardial infarction occurs in 6% of the cases with chest pain due to cocaine use [26] regardless of the route of administration [27]. The electrocardiogram may be abnormal in 56 to 84% of patients with chest pain after the cocaine use in the absence of AMI, and half of these patients present serum elevation of creatine phosphokinase (CPK) presumably due to rhabdomyolysis. The diagnosis of acute myocardial infarction in cocaine users who present to the emergency room for chest pain should be carried out based on serum troponin levels [28].

The pathogenesis of ischemia and AMI related to cocaine is multifactorial [26-29]:

- stimulation of alpha and beta adrenergic receptors leads to coronary arteries vasoconstriction and tachycardia, producing an increase in the myocardial oxygen demand and contractility in the presence of insufficient blood flow due to vasoconstriction;
- direct myocardial toxicity with blockade of the sodium channels, causing a decrease of the depolarization slope and conduction velocity, with lengthening of the PR, QRS and QT intervals, which can lead to myocardial dysfunction, hypotension and arrhythmia;
- accelerated atherosclerosis and thrombosis by increased plasminogen activator inhibitor, platelet activation and endothelial permeability.

There is increasing evidence of the chronic effects of cocaine on the coronary arteries, due to its thrombogenicity and acceleration of the arteriosclerosis process, which places it as a major coronary risk factor [7]. Chronic cocaine abuse causes left ventricular hypertrophy probably due to the transient elevation of blood pressure after cocaine consumption and systolic dysfunction. Chronic consumption may also be responsible for the cardiomegaly.

The most representative cardiovascular anatomo-pathological findings associated with cocaine are the presence of myocardial necrosis strands [29-32] associated with structural changes that increase the risk of arrhythmias and sudden death as well as the presence of interstitial edema. Prolonged cocaine use has also been associated with the development of dilated cardio-myopathy [30].

In our case, cocaine and benzoylecgonine doses were higher than the one considered lethal by Repetto et al. [21] and Musshoff et al. [22]. Both the cardiomegaly and the hypertrophy of the left ventricle that we discovered are compatible with the chronic use of cocaine as it can be seen from the consulted literature. The levels of cTnI were much higher than the values that are clinically considered as indicative of acute myocardial infarction which indicates the presence of myocardial necrosis in the absence of significant coronary lesions.

Conclusions

The autopsy, together with the results of the complementary tests, indicate that the most probable death mechanism has been a cardiogenic shock secondary to extensive myocardial necrosis due to cocaine intoxication. The death occurred fast after cocaine overdose and alcohol consumption.

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