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DEATH AS A CONSEQUENCE OF CARDIORESPIRATORY ARREST CAUSED BY COCAINE-INDUCED GENERALIZED SEIZURE: TOXICOLOGICAL DATA IN A CASE REPORT

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Abstract: Consumption of cocaine can induce seizures, typically in the form of generalized tonic-clonic convulsions, that resolve spontaneously without neurological disease. In a minority of cases, cocaine-induced seizures can lead to death. In the literature, data concerning cocaine concentrations that can induce seizures are extremely scarce, and, to our knowledge, there are no studies reporting concentrations of cocaine and its metabolites in organs in cases of death resulting from cardio-respiratory arrest during epileptic seizures induced by cocaine. We present the case of a 26-year-old subject who died as a consequence of cardiorespiratory arrest induced by a generalized epileptic seizure, which occurred approximately 12 h after nasal cocaine intake. Toxicological analysis of samples collected during autopsy, performed 3 days after his death, revealed a concentration of 30.43 ng/mL of cocaine and 222.44 ng/mL of benzoylecgonine in the blood, less than the amount in which an overdose occurs, and 487.90 ng/mL of cocaine and 16285.28 ng/mL of benzoylecgonine in urinary samples, that allowed us to affirm that the subject at the time of development of the crisis had already metabolized a quantity of the drug.

Keywords: cocaine induced seizures, epilepsy, death, cocaine.

INTRODUCTION

Cocaine is a drug extracted from erythroxylon Coca leaves [1]. It causes an increase in monoamine concentration (dopamine, norepinephrine, epinephrine, and serotonin), inhibiting their re-uptake transporters, resulting in enhanced and prolonged sympathetic effects [2]. It induce intense peripheral vasoconstriction, an increase in blood pressure and heart rate, mydriasis, and sphincter contractions [3]. The effects sought by the use of this substance consist of increased concentration, euphoria; at major doses, anxiety, agitation, paranoid psychosis and aggressive behavior can occur [2].

The onset of epileptic crises is a manifestation of cocaine induced toxicity [2-5]. Generally, seizures caused by cocaine consumption are diagnosed excluding other possible causes, such as cranial trauma and cerebral bleeding. Toxicological analysis confirmed this diagnosis.

According to the literature, seizures caused by cocaine consumption consist of generalized tonic-clonic crises, which generally resolve spontaneously [2-7]. These episodes can manifest equally in subjects without previous epileptic crises in their medical history and in individuals affected by epilepsy [3-5].

Cases of death that occurred as a result of epileptic crises induced by cocaine intake have been described in the literature [1, 8]. However, studies on cocaine and its metabolites concentrations in the blood that are capable of inducing seizures are rare [3]. To our knowledge, there are no studies reporting the concentrations of cocaine and its metabolites in organs in cases of death resulting from cardio-respiratory arrest during epileptic seizures induced by cocaine.

The purpose of the present study is to present a case of death in a 26-year-old subject due to cardiorespiratory arrest, resulting from a cocaine-induced seizure, providing toxicological data regarding the doses at which the crisis developed.

CASE REPORT

As stated by some friends, at around 10:00 pm, a 26-year-old boy, drank alcohol and snorted cocaine (6 or 7 strips) after having dinner. The day after, at around 12:00 am, he woke up complaining of an intense

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headache and nausea. After 1:00 pm he developed tonic-clonic seizure, as inferred by the pathologist who subsequently performed the autopsy from the description provided by witnesses. Rescuers arrived on site at 1:35 pm found the subject in cardiorespiratory arrest. Despite the RCP maneuvers, the subject was declared dead. Autopsy was performed 3 days after the death.

Hypostasis was present on his face, upper chest and limbs. Upon opening of the chest, the lungs covered the pericardium. Pleural spaces were empty. The right lung had a regular shape, increased consistency and volume, reddish color and weighed g 500. The left lung had a regular shape, increased consistency and volume, a reddish color, and weighed g 400. The large and medium bronchi were intact, without foam inside; the arterial and venous vessels had intact walls. The heart had regular shape, volume, and consistency. Nothing else relevant was detected during autopsy. Organs and biological fluids samples were then collected for subsequent toxicological analyses. For all samples, qualitative and quantitative analyses by gas chromatography with mass spectrometry (GC-MS) were performed according to the literature guidelines [8]. Results are reported in Table 1.

Toxicological analysis of the nasal swab revealed traces of cocaine. No other drug was detected. The cause of death was attributed to cardiorespiratory arrest resulting from cocaine-induced seizures.

DISCUSSION

Seizures are a possible side effect of cocaine use [2-5]. Winbery *et al*. [3] highlighted that epidemiological data oscillate between 1% and 29% of cocaine users, ascribing this high variability to different habits of drug consumption (occasional or habitual) and the presence of other concomitant causes of epileptic crises, including the consumption of other drugs or alcohol. Buttner *et al*. [2], referring solely to habitual cocaine users, reported a frequency of cocaine-induced epileptic crisis between 2% and 10%. This data does not contrast with those reported by Majlesi *et al*. [4] and Koppel *et al*. [9] referring to hospital accesses in cases of cocaine intoxication: according to the first author, epileptic seizures were found in 8% of the total, while for the second in 3% of the examined sample.

Table 1.

Sample	Cocaine (ng/ml)	Benzoylecgonine (ng/ml)
Blood	30.43	222.44
Urine	487.90	16285.28
Bile	325.40	2621.90
Liver	8.72	312.93
Lung	34.58	255.29
Brain	25.31	111.99
Heart	10.66	346.56
Spleen	20.14	316.92
Kidney	5.48	406.42

Different mechanisms for the development of cocaine-induced epileptic seizures have been hypothesized, including repression of central nervous systems inhibitors, including the Gabaergic system [10], increase in serum serotonin levels, and progressive cocaine sensitization, defined as kindling [10]. According to this phenomenon, due to repeated intake of cocaine at "sub-convulsive" constant doses, a subject has a greater predisposition to develop epileptic seizures, even at doses that, if taken sporadically, would not induce this side effect [4, 5, 11-13]. Regarding the routes of administration, Dhuna *et al*. [5] confirmed that intravenous administration of cocaine is more related to the development of seizures than smoking and snorting.

It should also be noted that other causes can intervene in the development of epileptic seizures in cases of cocaine intoxication. Thus, Winbery *et al*. hypothesized that epileptic crisis could be related to drug impurities or substances used to cut the drug [3].

As previously reported, most cocaine-induced epileptic seizures resolve spontaneously without neurological disease. Nevertheless, seizures that caused death have also been described in the literature. Death can occur for respiratory paralysis or following the development of arrhythmias, including atrial or ventricular tachyarrhythmia, asystole, bradycardia or atrium-ventricular blocks [1, 4, 9, 14]. It should also be emphasized that the sympathomimetic effects of cocaine precipitate the conditions of a patient with comorbidities, such as myocardial ischemia, hypertension, or cerebral bleeding [1].

We present the case of a 26 years old subject who developed seizures approximately 12 h after snorting cocaine. This datum is in line with the findings of Alldredge *et al*, who reported that drug-related seizures developed within 24 h of cocaine intake [7].

Regarding toxicological data, as previously stated, studies dealing with cocaine and its metabolites concentrations in the blood capable of inducing seizures are rare [3]. To our knowledge, no studies have reported the concentration of cocaine and its metabolites in organs in cases of death resulting from cardio- respiratory arrest during epileptic seizures

caused by cocaine.

Only Winbery *et al*. [3] reported data related to toxicological analysis conducted on the whole blood of two subjects who developed epileptic seizures after cocaine consumption. It must be specified that these data refer to subjects who survived the crisis. The authors described the plasma concentration of cocaine detected 30 min before a crisis in subject 1 and an hour after an epileptic seizure in subject 2, that resulted respectively: 2.48 mg/ l and 2.87 mg/ l respectively, and the values of benzoylecgonine were 4.997 mg/ l and 4.60 mg/ l.

In our case toxicological analysis performed on samples collected during autopsy revealed a concentration of 30.43 ng/mL of cocaine and 222.44 ng/mL of benzoylecgonine in the blood, less than those in which an overdose occurs [15-16] and 487.90 ng/ ml of cocaine and 16285.28 ng/mL of benzoylecgonine in urinary samples, that allowed us to affirm that the subject at the time of development of the crisis had already metabolized a quantity of the drug.

In contrast, Ritz and George [13] affirmed that cocaine did not produce seizures at cocaine doses up to 320 mg/kg. Koppel *et al*. described the development of epileptic seizures in the case of erroneous cocaine intake during body packing, not specifically reporting blood cocaine concentration, assuming that these were high because of the breaking of drug packets inside the body [9].

In the case we presented, regarding a subject accustomed to cocaine abuse and who had already metabolized part of the substance, the development of a seizure could therefore be explained by the already mentioned kindling phenomenon [10-17].

In conclusion, studies that report the concentrations at which cocaine-induced epileptic seizures occur are extremely rare. The scarcity of data could be explained by the fact that, in most cases, crises resolve spontaneously without the development of neurological disease or death. The absence of univocal toxicological data can also be explained by the kindling phenomenon, which lowers the threshold value for inducing epileptic seizures in habitual cocaine users.

Conflict of interest

The authors declare that they have no conflict of interest.

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