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Reporte de caso

Ischemic stroke related to acute consumption of cocaine

Infarto cerebral por consumo de cocaína

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Abstract

Cocaine is one of the most common used psychomotor stimulants in the world. It's often used during the second and third decade of life. Nowadays, cocaine abuse in Colombia is rising, with negative effects for the consumer´s health and making it a problem of public health. Cardiovascular diseases are the most common side effects related to cocaine abuse. However, adverse neurological effects remain to be a very important cause of morbidity and mortality. Particularly, the risk of ischemic stroke might be up to seven-fold higher in cocaine users in comparison to non-users. In the following report, we describe the case of a 22-year-old man who presented to the emergency department with a hemispheric ischemic stroke secondary to cocaine intake. Next, we review the key toxicological aspects and the physiopathology of this neurological complication, with special emphasis in the effect of the toxic metabolite "norcocaine", which can explain most of the adverse neurological outcomes. Finally, we review the therapeutic options for cocaine induced ischemic stroke.

Keywords: Cocaine; Ischemic stroke; Complications.

Resumen

La cocaína es una de las sustancias sicomotoras más usadas en el mundo. Es comúnmente utilizada durante la segunda y tercera década de la vida. Actualmente, el abuso de cocaína en Colombia está en aumento, con efectos negativos para la salud del consumidor, además de estar convirtiéndose en un grave problema de salud pública. Los efectos adversos más comunes del abuso de cocaína son los efectos cardiovasculares. Sin embargo, los efectos adversos neurológicos continúan siendo una importante causa de morbilidad y mortalidad. Particularmente, el riesgo de ataque cerebro vascular isquémico podría aumentarse siete veces más en pacientes consumidores de cocaína comparado con pacientes no consumidores. En el siguiente reporte de caso, describimos el caso de un paciente de 22 años, quien ingresó al servicio de urgencias con un ataque cerebro vascular isquémico secundario al uso de cocaína. Posteriormente, discutimos los principales aspectos toxicológicos y la fisiopatología de esta complicación neurológica, con énfasis especial en los efectos tóxicos del metabolito activo norcocaína, el cual pudiera explicar la mayoría de los efectos cardiovasculares adversos. Finalmente, planteamos el enfoque terapéutico del ataque cerebro vascular isquémico secundario a cocaína.

Palabras clave: Cocaína; Ataque cerebro vascular isquémico; Complicaciones.

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Introduction

Cocaine is an alkaloid drug used by nearly 14 million people around the world, mainly in the second and third decade of life, which represents 0.3% of the global population between 15 and 64 years old (1).

In the United States of America, 6.5 million people are active drug users. In Colombia, the prevalence of cocaine intake is 1.8%. It is most common among males. The most prevalent age is in older than 12 years old (2). In our country, the prevalence increased significantly, with a prevalence of occasional cocaine intake during the last year of 2.5% in men and 1.3% in women. In average, 2.8% of currently enrolled undergraduate students have tried the cocaine at once, 1.9% have used it over the last year and 1% have tried it over the last month (3).

The abuse of this illegal substance increases the risk of pathologies in multiple systems. The incidence of ischemic stroke is relatively uncommon. Thus, clear guidelines regarding clinical management are not widely available. It is mandatory to search for review articles or expert consensus to broad knowledge about this specific and forgotten topic. This lack of scientific evidence is the reason behind our interest of writing this case report about cocaine induced ischemic stroke and explain in detail the relationship between stroke and the acute intake of cocaine.

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Case description

A 22 years-old male inmate at the local prison developed a seizure episode. He was evaluated by a rapid response team and transferred to the local hospital. His medical history was remarkable for hypertension and cocaine abuse. He was not compliant to his blood pressure medications. At admission, he was in bad overall conditions, with Glasgow Coma Scale of 9/15 (values not specified).

The physical examination was inclusive of right hemiplegia associated with motor and sensitive aphasia. He received 100 mg of intravenous (IV) phenytoin for seizures management. Laboratory tests and images were done at admission. Computerized Tomography (CT) scan showed an ischemic region in the left medial cerebral artery region, with increased cerebral edema and cerebral midline displacement of 9 mm, located in the subfalcine region. In addition, he had compression of the peri-mesencephalic cisternae. We didn't include CT scan images because this was a retrospective case and the CT scan images were not available anymore in the medical records. However, CT scan report was included in the patient' s medical record.

The drug analysis was positive for cocaine and tetrahydrocannabinol. Basic metabolic panel (BMP) was remarkable for the following: Creatinine phosphokinase (CPK) of 1321 mU/mL (reference range, 32-162), creatinine of 1.18 (reference range, 0.5-1.3), Blood Urea Nitrogen (BUN) of 16.3 mg/dL (reference range, 5-20), partial pressure of oxygen (PaO_2) was 34.7 and Pa/Fi of 165. Eight hours after the first seizure, he was referred to a third level complexity hospital for management in a neurologic intensive care unit.

At admission, left hemispheric ischemic stroke was diagnosed with an adrenergic toxidrome in resolution and acute intoxication with cocaine chlorohydrate and tetrahydrocannabinol. The patient was found to be stable, with a Richmond Agitation Sedation Scale (RASS) of -5 (reference range, -5 to +5), miotic pupils without motor response and weak distal pulses in four extremities. Blood glucose levels were 95 mg/dL (range

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of reference, 60-100). Control of basic metabolic panel was normal and the blood arterial gases showed improvement of the Pa/Fi, which changed from 165 to 347. Troponins were positive, but there was not a troponin curve done. Creatinine phosphokinase continued increasing, reaching a value of 2625 after multiple crystalloid infusions. A control CT scan was performed but failed to show new pathologic findings. Neurosurgery was consulted because of the possibility of decompressive craniotomy.

After Neurosurgery evaluation, they conclude that due to the high grade of local ischemic compromise, the high-generalized edema and the possible compromise of the left carotid artery, he was not a suitable candidate for surgical intervention.

The day after, the toxicology team evaluated the patient. Physical exam was remarkable for absence of gag reflex and presence of Babinski reflex in the left side. Tendinous reflexes of the four extremities were conserved. Unfortunately, the patient turned unstable and coded. Despite CPR protocol, he passed away. The conclusion was that the ischemic stroke was secondary to the vasospastic effect induced initially by norcocaine, a toxic metabolite product of N-methylation of cocaine. It´s very likely that the metabolite caused not only central nervous system damage but also hepatic and cardiac damage.

The neurotoxic mechanism of norcocaine is explained by two reasons: First, it crosses the blood brain barrier; therefore, it can easily penetrate to the central nervous system. Second, it has significant metabolic activity.

Discussion

Cocaine is a stimulant alkaloid often used as a recreational drug. Cocaine is made-up of an alkaloid called benzoyl-methyl-ecgonine, a lipophilic compound metabolized by three different pathways which are affected by genetic and acquired factors (1). First, a 50% of the benzoyl-methyl-ecgonine is metabolized by the enzyme methyl-esterase and by spontaneous hydrolysis. These two metabolic steps end-up in benzoyl-ecgonine. Second, the enzyme butyl-cholinesterase metabolizes the other 30-50% to form ecgonine-methyl-ester. These two metabolites (benzoyl-ecgonine and ecgonine-methyl-ester) have low pharmacological potency. Finally, the third pathway is the N-demethylation process which ends with a strong neurotoxic end product known as "norcocaine". This metabolite is mainly responsible for the neurovascular pathogenicity of cocaine (3).

The neurotoxic mechanism of norcocaine is explained by two reasons: First, it crosses the blood brain barrier; therefore, it can easily penetrate to the central nervous system. Second, it has significant metabolic activity. This metabolite is also involved in cardiac toxicity and hepatic toxicity. In addition, a fourth toxic metabolite may appear if concomitant use of ethanol. This process occurs because of a trans-esterification process of ethanol and cocaine (4).

The main complications of the acute intake of cocaine are secondary to the vasospasm. Among the main cardiovascular complications, acute coronary syndrome and arrhythmias are the main clinical manifestations (5). In addition, the neurological complications include seizures, transient ischemic deficit and neurovascular pathologies, mainly the ischemic and hemorrhagic stroke (5). So far, the evidence highly supports the direct relationship between acute cocaine intake and incidence of stroke (6).

The risk of ischemic stroke can be seven times higher in people that consume cocaine in comparison to those who don't. The average age of incidence for stroke is 30.5 ± 12.1 years, being most prevalent among males (76%). The incidence of stroke varies depending on the etiology. Hemorrhagic stroke is more prevalent (78%) com-

pared to ischemic stroke (22%). According to previous results obtained from Petitti *et al*., who analyzed a cohort of 347 patients with a diagnosis of stroke confirmed by CT scan, with mean ages ranging between 15 to 44 years old, they found that seven of them had a positive urine test for alkaloids (most likely cocaine). In their study, they concluded that cocaine was a strong risk factor for stroke (7).

Cocaine acts by inhibiting biogenic amines reuptake. In addition, it enhances release of more neurotransmitters, which are stored in synaptic vesicles. These two effects cause an inappropriate increase in the concentration of excitatory neurotransmitters in the presynaptic membrane, mainly the dopamine (8). Adrenergic receptors in the autonomic sympathetic system is stimulated (Alpha and Beta-adrenergic subtype receptors) provided the accumulation of catecholamine, which have a direct vasoconstrictor effect and rise in blood pressure secondary to Protein Gq activation, mediated by Alpha receptor. Inotropism and chronotropism are also present, mediated by Protein Gq activation, secondary to Beta-receptor (9). A decrease in the nitric oxide production and an increase in the release of Endothelin-1 will cause vasospasm, increase in oxygen extraction and consumption by tissues (9).

The risk of ischemic stroke can be seven times higher in people that consume cocaine in comparison to those who don't.

Regarding the effect of this metabolite in ionic channels, is has a direct effect in Calcium channels by stimulating the release of intracellular calcium in the sarcoplasmic reticulum of the *Muscularis Lisa* layer in the cerebral arterial vasculature (6). These consequences in the arterial vasculature imply a great metabolic demand and create an adequate environment for an ischemic stroke to happen (10).

Cocaine intake causes pathologic changes in the arterial vasculature itself. It enhances a prothrombotic effect that increases the risk of thrombi to occur and thus, an obstruction (11). On the other hand, chronic intake of cocaine induces changes in the cerebral vasculature and disruption of the laminar flow, enhancing platelet aggregation (12).

Pathology findings are consistent with a disruption of the Tunica media layer and peri-arteriolar fibrosis in the arterial vasculature of the nasal mucosa and intimal hyperplasia of the coronary arteries (13). According to recent findings, there is not conclusive evidence that histologic changes secondary to cocaine induced vasospasm take place in arterial vasculature.

Regarding the initial approach to ischemic stroke secondary to cocaine intake, it is solely based on the same therapeutic principles as other ischemic strokes of different etiologies (14). The main treatment goal is based on the window period that enables the patient to receive or not fibrynolitic therapy, which kind of fibrynolitic and determines the best diagnostic test. The acute treatment is intended to use of fibrinolysis therapy as soon as possible, whenever the patient remains in a suitable therapeutic window. Correspondingly, subacute treatment is oriented towards the use of dihydropyridine calcium channel blockers (15).

Initially, a suitable approach is elementary pre-hospital treatment, where a stabilization of the patient must be pursued. It is necessary to guarantee oxygen saturation greater than 94% and a systolic blood pressure that varies based on the therapeutic strategy. Nonetheless, a safe standpoint is to guarantee blood pressures below 185/110 mm Hg in the acute setting whenever the patient is intended to undergo acute reperfusion therapy (14). The reason behind this rationale is that the ongoing edema increases the intracranial pressure and diminishes the cerebral perfusion

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pressure. Consequently, cerebral blood flow is reduced whenever the arterial blood pressure is too low. However, arterial blood pressure above 185/110 mm Hg has been defined as the upper limit for performing acute reperfusion therapy since it showed better outcomes.

Once the patient is admitted to the Emergency Room, it is necessary to perform a brain image within the first 30 minutes after presentation (16). CT scan is a suitable option; this is followed by the decision of reperfusion therapy. Thrombolysis can be achieved in two separate ways: Pharmacologically or with intra-arterial endovascular therapy. The former, consist of an intravenous infusion of thrombolytic agent. The latter, is usually done using a catheter that goes intra-arterial and release a thrombolytic agent. Some of those catheters, depending on the generation, may directly disrupt the thrombi (17). The catheter specifications go beyond the scope of this article. The decision between both therapies relies on the window period (18).

If the time between the ischemic episode and the expected time of reperfusion is lesser than 4.5 hours, a pharmacological strategy must be pursued. If the timing goes from 4.5 - 6 hours, an intra-arterial endovascular strategy is recommended (14). In addition, if the thrombus is in a proximal branch of the anterior circulation, an endovascular strategy must be additionally pursued whenever the window period is below 6 hours. If the window period is below 4.5 hours, then both pharmacological and endovascular therapy must be performed.

CT scan is a suitable option; this is followed by the decision of reperfusion therapy. Thrombolysis can be achieved in two separate ways: Pharmacologically or with intra-arterial endovascular therapy.

Most authors agree that doing interventions once the window period is closed (more than 6 hours) is worthless and may be dangerous. In some clinical scenarios, reperfusion is done after 12 hours, particularly when the ischemic stroke is in the posterior circulation. Recent published clinical trials had suggested diminishing the reperfusion window period to 3 hours (16,17). Further studies are needed to include this recommendation in a consensus.

These recommendations based on window period and therapeutic strategies are is constant change, so we strongly recommend that the reader amplify his knowledge on the most recent guidelines. Moreover, different treatment classifications have been lately introduced based on the NIHSS scale. After deciding the reperfusion strategy, patient requires strict monitoring in a Neurologic ICU (18,19).

Once the acute setting is solved, sub-acute treatment involves measures targeted to suppress the vasospastic effect. For this purpose, dihydropyridine calcium channel blockers seem to be an adequate therapy because of its mechanism of action. Most of the trials were done using nimodipine, with positive results in very limited clinical scenarios. However, a systematic review published in Cochrane database which analyzed multiple prospective cohort studies suggested that nimodipine didn't have enough evidence to support its use in ischemic stroke (RR 1.07, 95% CI 0.98 to 1.17). Some of the secondary outcomes evaluated by this study, suggested that higher doses had a causal relationship with poorer outcomes (23).

One of the most important approaches to diminishing the morbidity of strokes is secondary prevention. It can reduce up to 80% the risk of presenting an ischemic stroke is most of the etiologies. Since this ischemic stroke is completely induced by cocaine, secondary prevention consists of avoiding cocaine consumption. There is no need of antiplatelet therapy or anticoagulation since the etiology is extrinsic (24).

There are some studies that suggest that isradipine, another dihydropyridine calcium channel blocker, might decrease the size of the necrosis. However, there are not clinical trials supporting this therapy (25). Nowadays, there is insufficient evidence to support a specific treatment in the sub-acute setting, especially when it is secondary to cocaine intake.

Neurological imaging may need to be done to monitor possible hemorrhagic transformation, especially if there is a large area of necrosis. The risk of hemorrhagic transformation is based on the classification degree (mild, moderate and severe). This classification is mostly important whenever the patient needs to be on anticoagulation, since it defines the period that the clinician should wait before resuming or starting a safe anticoagulation protocol.

Most common effects are cardiovascular and hepatic, but neurologic adverse effects are increasing since young people are starting to consume earlier and because this drug has become widely available.

Conclusions

Cocaine consumption can have multiple adverse effects in health. Most common effects are cardiovascular and hepatic, but neurologic adverse effects are increasing since young people are starting to consume earlier and because this drug has become widely available. As we show, neurologic mediated toxicity might cause poor outcomes. Further studies are needed to define a clear strategy for this specific type of ischemic stroke since there are not clear guidelines addressing this issue.

Conflicts of interest

The authors have nothing to disclose.

Financial disclosures

The authors have no financial disclosures.

Ethical issues

The patient´s records was taken from the hospital with permission of the hospital director and the Ethics committee. The records were collected retrospectively, therefore, patient´s approval wasn´t obtained. Confidential information and patient´s recognition is completely anonymous within the manuscript.

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