Capter 126

Awareness during anesthesia in cocaine addicters: concerning about chemical interactions

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ABSTRACT
The interaction between cocaine and anesthetic drugs has been known since 1884 when it was first used for the treatment of morphine addiction and as a local anesthetic. Due to a large number of users of the substance, the interaction with anesthetic drugs has been frequent and it has been seen that many drugs have their effects altered in the presence of cocaine. Through a bibliographical survey in PubMed and CrossRef, aiming to highlight the risks of this interaction and conduct in cases of elective surgeries in these patients, we conducted this study and verified that so many drugs have to be avoided due to their interaction effects, but in the absence of clinical signs of intoxication, screening becomes ineffective.

Keywords: anesthesiology, cocaine, drug interaction, psychotropic drugs, elective surgery.

1 INTRODUCTION

The discovery of cocaine by the German chemist Albert Niemann, in 1860, led to profound changes in the way surgeons promote invasive interventions in patients as suggested by Ball and Westhorpe (2003). However, in the following two decades it was observed that besides inducing addiction in consumers, this drug also had undesirable chemical interactions, as reviewed elsewhere (Ball and Westhorpe, 2003, Alraies *et al.*, 2011), including the potentiation of chemical substances that were used by anesthesiologists during surgery procedures. At that time, Sigmund Freud tested in a friend who was addicted to morphine the hypothesis that cocaine could also interact with this opioid and interrupt that addiction, this happened successfully but gradually was observed that the patients developed an addiction to cocaine (Niemann, 1860).

Over years, the number of patients using illicit drugs, mainly cocaine, has increased in the world, becoming common the presence of effects that, acutely or chronically could interfere with anesthetic management according to Alraires *et al.* (2011); however, the early diagnosis of cocaine poisoning continues being a challenge, as it is clinical, not correlating with toxicological tests, because its inactive metabolite takes about 6-14 days for complete elimination, making screening difficult as discussed by several authors (Weiss and Gawin, 1988, Lange and Hillis, 2001). According to different studies (Weiss

and Gawin, 1988, Ritz, Cone, and Kuhar, 1990), the effects of cocaine and its metabolites can generate synergistic interaction with anesthetics, as they act in synapses, involving neurotransmitters, a fact that can potentiate the sedation process or even decrease the metabolization of anesthetic drugs. In this context, it is important to evaluate and monitor these patients in surgeries to minimize the adverse effects of this drug interaction as suggested by Alraires *et al.* (2011).

2 MATERIALS AND METHODS

Here, we summarize the state of the art of literature exposing the risks of drug interaction between cocaine and anesthetic drugs, such as their harm to the patient and difficulties in perioperative management through this review. The search for publications was carried out in the electronic bibliographic database, such as PubMed. The descriptors used in the search were: anesthetic drugs, cocaine, and drug interaction. It was used as inclusion criteria for articles published as a systematic or narrative review. Duplicate books, dissertations, and studies were excluded.

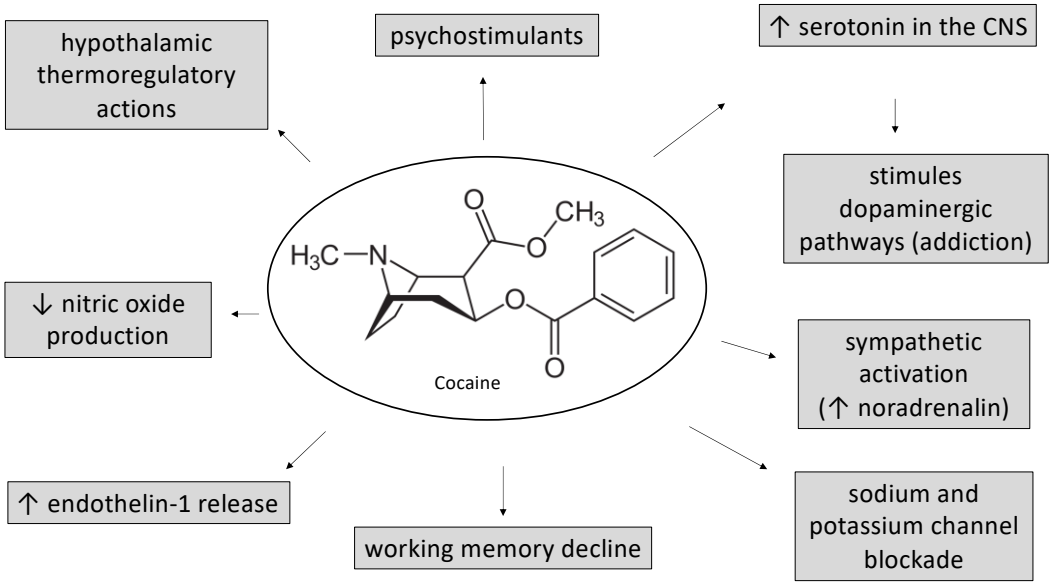
3 RESULTS

3.1 MECHANISM OF ACTION

Cocaine and its derivatives came from the plant *Erythroxylum coca.* Belonging to the class of alkaloids, this substance has psychostimulant properties (Tsuchiya, 2017). Due to its diversity of compounds, cocaine can be used in many routes, such as oral, nasal, pulmonary, or intravenous route (Corrêa *et al.*, 2014). As for its pharmacokinetics, cocaine is a benzoylmethylenoin, with a plasma half-life of about 30-60 min, suffering hydrolysis by plasma and hepatic esterases, producing inactive metabolites (Ball and Westhorpe, 2003), such as ecgonine methyl ester, which by degrading forms benzoylgonin, a urinary metabolite and Norcaide, a metabolite produced through demethylation (Luft and Mendes, 2007).

Cocaine is considered a psychostimulant drug with a mechanism of action due to the combination of increased production of catecholamines (dopamine, norepinephrine) and serotonin; and inhibition of the reuptake of these substances with emphasis on the increasing availability of dopamine, a mechanism that explains the stimulant and addictive effects of the drug, in addition to the double effect on α and β-adrenergic receptors, a fact that corroborates the presence of cardiopathies in these patients [Fig 1] (Alraies *et al.*, 2011). As a second effect, cocaine has a class I antiarrhythmic effect, blocking sodium and potassium channels, and preventing the spread of action potential (Fozzard *et al.*, 2005, Tsuchiya and Mizogami, 2013). Although it has paradoxically opposite mechanisms of action, its psychostimulant effect is corroborated by the greater intensity of action in the pre-synaptic terminals to the detriment of the antiarrhythmic effect (Lange and Hillis, 2001).

Figure 1. Demonstration of the different sites of action of Cocaine. Adapted from Alraies, MC., Alraiyes AH. and Michota F., 2011. Should surgery be canceled when surreptitious cocaine use is discovered before elective non-cardiac surgery? Middle East Journal of Anaesthesiology, 21(3), pp. 445-446.



3.2 INTERACTION OF COCAINE AND ANESTHETIC DRUGS

Cocaine, because of its paradoxical effects, provides great concern in the case of surgery. Anesthetic drugs, such as ketamine, increase the circulation of catecholamines, and the additive interaction to cocaine, can lead to overstimulation of α and β receptors, which may culminate in cardiovascular events (Vadivelu *et al.*, 2014) as well as halothane, a halogenated anesthetic that sensitizes the catecholamine conduction system in the myocardium, and when used in cocaine addiction, can generate prolongation of QT interval and arrhythmias (Alraies *et al.*, 2011, Tsuchiya, 2017). We should also avoid other drugs that can increase QT interval, such as methadone and ondansetron [Table 1]).(Ehret *et al.*, 2006, Roden, 2004, Dolenska, 2009)

Table 1. Relationship Between Classes of Drugs used in Anesthesia and their cardiovascular risk in cocaine users.

Drugs		Cardiovascular adverse effect
Anesthetic	Ketamine	Release of catecholamine sensitizing the myocardium to
	Halogenated	catecholamines and contributing to the increased incidence of arrhythmias in these patients (ventricular tachycardia, ventricular extrasystole and ventricular fibrillation) Arterial hypertension
β-blockers	Labetalol Propranolol	Increased incidence of ventricular arrhythmias Arterial hypertension A complication of blood pressure control during surgery
a2-adrenergic agonist	Dexmedetomidine	Hypertensive events Possibility of relative hypovolemia with lack of response to vasopressor's action
Vasoactive medications	Sodium nitroprusside	Higher incidence of ventricular arrhythmias
Opioids	Methadone	Prolongation of QT interval and arrhythmias
Selective serotonin 5-HT3-receptor antagonist which antiemetic activity	Ondansetron	Prolongation of QT interval and arrhythmias
Muscle relaxers	Succinylcholine	Increasing the serum concentration of both (cocaine and succinylcholine) and risk of the arrhythmias

In general anesthesia, the challenge for cocaine users is the control of arterial hypertension, since it is not indicated to administer β-blockers alone (Moran *et al*.,2015), because they potentiate α-agonism, giving priority to other vasodilators (Kuczkowski, 2003, Kuczkowski, 2004, Gazoni *et al*., 2006). An excellent option would be pressure control with Dexmedetomidine, an a2-adrenergic agonist (Moran *et al*, 2015). Despite the risk of hypertensive events, general anesthesia is preferred over local anesthesia due to the possibility of relative hypovolemia with a lack of response to the vasopressor's action, in addition to combative behavior, altered pain perception, and cocaine-induced thrombocytopenia (Hill, Ogunnaike and Johnson, 2006, Luft and Mendes, 2007), besides the additive effect to local anesthetics, with risk of toxicity, since the safe dose is unpredictable (Corrêa, *et al*., 2014) and also because seizures by cocaine use do not decrease with anticonvulsant drugs or inhalation anesthetics (Luft and Mendes, 2007).

Regarding the use of muscle relaxers, succinylcholine, a depolarizing relaxant, presents a prolonged response in chronic users, due to the reduction of pseudocholinesterase, responsible for its metabolization, but in cases of acute intoxication, this fact occurs by the competition of cocaine with succinylcholine in metabolism, increasing the serum concentration of both [Table 1] (Fleming *et al*, 1990; Alraies *et al.*, 2011).

4 DISCUSSION

Surgeries in cocaine users have increased in frequency, but despite all the important risks of drug interaction, studies have shown that since these patients show no signs of substance poisoning, the risk of a perioperative complication does not increase when compared to a non-user individual (Alraies *et al.*, 2011). Given that toxicological tests can present a result that does not match intoxication by the substance, as the elimination half-life of its inactive metabolite is up to 14 days, the only exclusion criterion for elective surgery would be clinical symptoms, such as excitation, weight loss, anxiety, requests for sedatives or

opioid and digestive problems, to prevent cocaine interaction problems in the body (Vadivelu, *et al.*, 2014).

Cocaine has two important actions: psychostimulant and antiarrhythmic. The antiarrhythmic action, with double effect in α and β-adrenergic receptors, leads to an important interaction with ketamine due to the release of catecholamines, as well as halogenates, sensitizing the myocardium to catecholamines and contributes to an increase in the incidence of arrhythmias in these patients. Because cocaine interacts with catecholamines and nitric oxide, it is important the awareness of interactions with commonly used drugs during anesthesia, such as beta-blockers, sodium nitroprusside and consequently complicating the control of blood pressure during the surgery [Table 1] (Bijker *et al.*, 2007). Despite that, Moon *et al.* (2019), conducted a retrospective cohort study, in which it was found that cocaine addicts do not need increased anesthetics or had a higher incidence of ventricular arrhythmias, with only higher blood pressure scores requiring vasodilators. These data emphasize the need for follow-up of these patients to minimize the effects arising from the drug-drug interaction presented in these cases.

However, the possibility of drug interaction leads us to reflect on whether important interaction effects with other anesthetics have gone unnoticed over the years.

Patients presenting acute or chronic intoxication by drug abuse are an additional concern for the anesthesiologist and surgeons during and after an operation, which sometimes it is possible to delay the scheduled surgery but on other occasions, the patient needs an urgent or emergent intervention, and both surgeon and anesthesiologist must be able to deal with the undesirable changes that may occur in these patients. Preoperative targeted questions to the patient regarding drug use can help surgeons and anesthesiologists to know the screening for drug addiction and can allow them to better take care of the patient during and in the postoperative intervention.

Evidence shows that there are important interactions that can complicate the perioperative period, however, these patients do not present higher risks of complications than the general population as a more recent study (Moon *et al.*, 2020) has shown, corroborating the possibility of performing non-cardiac elective surgeries in these patients, if they do not show signs of intoxication, avoiding unnecessary postponement of surgical procedures (Ball and Westhorpe, 2003, Gazoni *et al.*, 2006).

DECLARATION OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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