

Crack: pharmacokinetics, pharmacodynamics, and clinical and toxic effects

Crack: *farmacocinética, farmacodinâmica, efeitos clínicos e tóxicos*

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ABSTRACT

This review presents the chemical and pharmacological aspects of crack in addition to its clinical and toxicological effects. Studies published between 1990 and 2012 were evaluated through systematic searches in the Scielo, Lilacs, and electronic journals databases available on the internet. Cocaine is the active substance in crack, derived from *Erythroxylum coca* plant leaves. Regardless of its form of consumption (intravenous, inhalation, oral, and intranasal), it exerts toxic effects from its main metabolites: benzoylecgonine and ecgonine methyl ester. The high fat solubility presented allows their crossing of the blood-brain barrier and placenta with a special affinity for the brain. It acts as a potent adrenergic, dopaminergic, and serotonergic agonist, and voltage-dependent sodium channels blocker, which justifies its potential clinical and toxic effects. Acute intoxication will manifest in the hyperactivity of these systems. The understanding of crack toxicology is important for the detection and clinical management of acute poisoning, abstinence, and consequences of chronic use.

Key words: Crack Cocaine; Crack Cocaine/pharmacokinetics; Toxicology; Pharmacology.

RESUMO

*Esta revisão apresenta os aspectos químicos e farmacológicos do crack, além de seus efeitos clínicos e toxicológicos. Foram abordados trabalhos publicados entre os anos de 1990 e 2012, por intermédio de buscas sistemáticas utilizando o banco de dados Scielo, Lilacs e jornais eletrônicos disponíveis na internet. O crack possui como substância ativa a cocaína, derivada de folhas da planta *Erythroxylum coca*. Independentemente da sua forma de consumo (intravenosa, inalatória, oral e intranasal), exerce seus efeitos tóxicos a partir dos principais metabólitos: benzoilecgonina e metil-éster de ecgonina. A alta lipossolubilidade apresentada permite que atravesse a barreira hematoencefálica e placentária, tendo especial afinidade pelo cérebro. Atua como potente agonista adrenérgico, dopaminérgico e serotoninérgico e bloqueador dos canais de sódio voltagem-dependentes, o que justifica seus efeitos clínicos e potencial tóxico. A intoxicação aguda irá se manifestar pela hiperatividade desses sistemas. O entendimento da toxicologia do crack é importante para detecção e manejo clínico da intoxicação aguda, da sua abstinência e consequências do seu uso crônico.*

Palavras-chave: Cocaína Crack; Cocaína Crack/farmacocinética; Toxicologia; Farmacologia.

INTRODUCTION

Popularly and commercially, the name cocaine refers to cocaine salts (cocaine hydrochloride and cocaine sulfate), which are both the most pure products of the re-

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fining process of coke (made from the leaves of *Erythroxylum coca*). Cocaine salts are heat-resistant, low-volatile, and with a melting point at 190°C. They are known as “dust”, “talc”, “snow”, “flour”, and “bright white” (Figure 1).¹⁻³

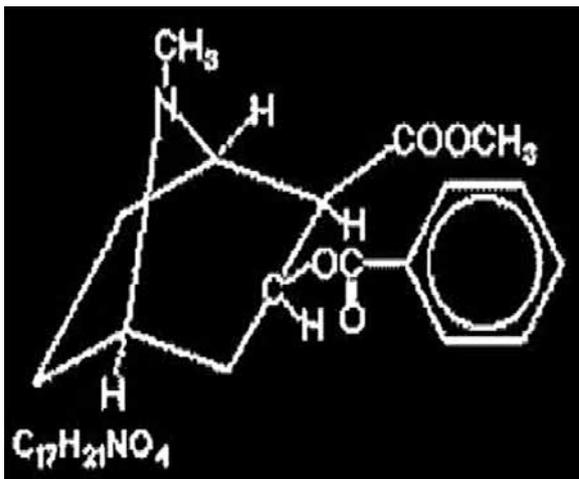


Figure 1 - Chemical structure of cocaine.
Source: Mosquera and Menéndez MC.¹

What is called base paste or cocaine paste is a white, brownish substance, semi-solid or solid, obtained as the intermediate product in the refining of cocaine salts. It is a crude product, which contains many impurities such as methanol, ether, acetone, potassium permanganate, benzoic acid, kerosene, gasoline, and sulfuric acid, and is termed basuco or crack.^{1,2,4}

Crack is obtained from the mixture of coca base paste or refined cocaine with baking soda and water. When heated above 100°C, it undergoes a decantation process in which liquid and solid substances are separated. The cooling of the solid portion generates the crack rock, which concentrates the active ingredients of cocaine; it got its name from the crackling sound when smoked.²⁻⁶

This form of cocaine has the property to melt at 98°C and reach the boiling point at 250°C, which allows it to be smoked. Because it is produced clandestinely and without quality controls, the crack has differences in purity levels and may contain other toxic substances. Because of its impurities and aggregated substances, it costs less than cocaine and therefore, its consumption is higher in less economically favored groups.^{2,3}

PHARMACOKINETICS

Cocaine is well-absorbed by most routes of administration. The determination of these routes is important to characterize the speed with which it produces the beginning activity, blood concentration, and duration of the euphoric effect. The psychoactive effects are faster to onset when administered intravenously and inhaled compared to orally and intranasally. Cocaine salts are very diffusible in water and thermal labile allowing easy absorption through the nasal mucosa. Crack is insoluble in water but soluble in lipids and organic solvents; its main entry route is through inhalation.^{1,2,6}

The onset of psychoactive effects produced by cocaine takes between eight seconds and 30 minutes and remains between five and 90 minutes partially depending on the route of administration. Crack shows activity between an average of six and eight seconds and lasts between five and 10 minutes. When injected, the drug takes twice as long to start acting. The duration of the cocaine effect is less when used intravenously and smoked, which means that the consumer has to manage multiple high doses to achieve a state of euphoria. The intravenous injection and inhalation of cocaine produce maximum plasma concentration levels after three to five and one to three minutes of the administration, respectively.^{2,5-9}

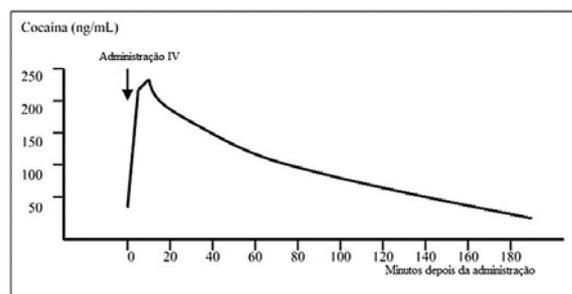


Figure 2 - Blood concentration as a function of time elapsed since intravenous administration.
Source: Pérez AO.⁹

When smoking crack, its active ingredient, which is cocaine, is rapidly absorbed by lung capillaries and goes into the bloodstream. Thus, cocaine is distributed throughout the body and, because its high lipid solubility it crosses the blood-brain and placenta barriers with a particular affinity for the brain.

Cocaine has a volume of distribution of 2 L/kg. The biotransformation of the active ingredient starts rapidly in the blood due to the pH in aqueous medium, which is enhanced by cholinesterases, and is subsequently completed in the liver where it is hydrolyzed by cholinesterases producing its major metabolites, the benzoylecgonine and methyl ester ecgonine. Other minor metabolites, such as norcocaine and cocaethylene (metabolite generated when cocaine is administered with ethanol) are also detected in smaller quantities.^{1,2,6}

Cocaine and its metabolites do not bind to plasma proteins. The average life of its metabolites varies between 4 and 6 hours and is longer than that of free cocaine, which is approximately 60 minutes. The amount found in the blood corresponds accurately to the quantity exposed to receptors. In people who had an overdose, the concentrations in the brain and blood are different and important; it can reach ten times more in the brain than in the blood when taken at the same time. It is eliminated primarily through the kidneys, accounting for 85-90% of the total. Of that amount, only 1 to 5% represents non-metabolized cocaine; benzoylecgonine and methyl ester ecgonine are the main forms found, detected six hours after consumption and with small amounts of the free form. Tests to verify the use of cocaine can be performed by analyzing blood, urine, and hair. The toxicological urine test is the reference test and identifies the benzoylecgonine metabolite, which can be detected between four and 48 hours after drug exposure.^{1,6,7}

PHARMACODYNAMICS

The effects of cocaine can be explained by its action on several receptors:^{1,2,7}

- blocks the voltage-dependent sodium channel exerting a local anesthetic effect by preventing the conduction of nerve impulses;
- operates in monoaminergic terminals, which inhibits the reuptake of dopamine, serotonin, and norepinephrine by competitively blocking their transporters. This action on transporters increases the amount of neurotransmitter in the synapse and stimulation on post-synaptic receptors. It is believed that the properties of the addiction to cocaine are primarily related to inhibition of the dopamine transporter;

- acts presynaptically on the vesicular dopamine transporter located in the mesolimbic and nigrostriatal nerve terminals responsible for storing the dopamine previously synthesized in the cytoplasm and/or dopamine recaptured in the synaptic cleft;
- has an affinity for sites in serotonergic, muscarinic (M1, M2), and sigma receptors.

The systemic effects occur as the result of the ability to simultaneously increase catecholamine levels and block its reuptake, which leads to a continuous antagonism in both receptors, alpha and beta. Cocaine exposure produces a myriad of symptoms and signs. Acute exposure can be associated with hyperthermia, hypertension, tachycardia, mydriasis, stupor and respiratory and cardiac depression; it also may obscure the classical response to trauma and hemorrhagic shock. In cardiac myocytes, it decreases the depolarization speed, breadth and conduction velocity of action potential possibly causing cardiac arrhythmias and sudden death. It provokes the sense of power and indefatigability; and at high doses it causes agitation, insomnia, hallucinations, and seizures. Chronic use is associated with the development of psychosis and paranoia. Both forms of cocaine, hydrochloride and free base (crack), have high potential to develop dependency.^{1,2,6,7}

TOXICOLOGICAL ASPECTS

Cocaine exerts its main effects through the dopaminergic, adrenergic, and serotonergic systems, which can be seen at:

- **dopaminergic system:** in the acute use, it prevents the reuptake of the neurotransmitter dopamine in the presynaptic cell in the mesocorticolimbic dopaminergic system and thus increases its availability in the synaptic cleft. This increased availability of dopamine neurotransmitters allows higher and more prolonged stimulation of the D1, D2, D3, D4, and D5 neuroreceptors. Many of the behavioral changes provoked can be attributed to this mechanism of action; however, it also induces the increased synthesis of dopamine. In contrast to these acute effects, the chronic use of cocaine causes dopamine depletion in the synaptic cleft;^{1,2}
- **adrenergic system:** the two major metabolites of cocaine, benzoylecgonine and ecgonine methyl ester, act as direct adrenergic agonists

in blocking the transport system in the nerve cell membrane, preventing the reuptake of the norepinephrine and epinephrine neurotransmitters in pre-synaptic cell, thereby increasing, the availability of these substances in the synaptic cleft.¹ This increased availability of adrenergic neurotransmitters allows higher and more prolonged stimulation of the α_1 , α_2 , and β_1 , β_2 , and β_3 adrenergic receptors. It also stimulates thyroxine-hydroxylase, which helps to produce more norepinephrine in the neuron. The norepinephrinic pathway is related to the alert and vigil systems. It is also related to hyperactivity of the autonomic system producing direct effects on the cardiovascular, endocrine, and ocular systems, and etc. Consequently, the following are observed: increased heart rate; vasoconstriction of arterioles and veins through the vascular smooth muscle; intense mydriasis by contraction of the radial muscle; increasing salivary, gastric, and pancreatic secretion, and intense sudoresis. This noradrenergic activation may be responsible for increasing blood pressure and vigil state due to an effect on the brain stem (locus coeruleus).² In addition to the adrenergic discharge that is initially produced, the stimulated production of the adenylyl cyclase enzyme and, therefore, increase of the cAMP second messenger from adenosine triphosphate (ATP) also occur, which generates an adrenergic response generally characterized by overall acceleration of physiological functions;¹

- **serotonergic system:** inhibits the reuptake of serotonin and its precursor, tryptophan, within serotonergic neurons. This action stimulates inhibitory presynaptic autoreceptors, increases the concentration of serotonin (5-HT) in the cleft, and causes negative retro-feeding, which rapidly depletes 5-HT in the brain. In general, the effect on 5-HT is inhibitory. This serotonergic pathway can relate to the hallucinatory and psychomimetic effects produced by cocaine, which explains the motor and stereotypic alterations seen in intoxicated individuals.¹

CLINICAL EFFECTS

- **neuropsychological effects:** cocaine and its derivatives have a broad effect on behavior and emotions, being highly prone to addiction by acting directly on the reward center. Its effect ranges from pathological emotions such as accentuated states of depression, grandiosity, and anxiety to paranoia and even severe affective disorders.^{1,4}

The action of one dose causes loss of appetite, transmit feelings of well-being, increases stamina by decreasing the feeling of fatigue, and promotes restlessness, excitement, talkativeness, anxiety, and even mental confusion. The initial euphoria can be followed by anxiety, agitation, delirium, psychosis, tremor, muscle stiffness or hyperactivity, and seizures.^{1,4}

The euphoria is phenomenally different from the euphoria produced by other substances (opiates, alcohol, etc.) and includes activation, initial anxiolytic effect, disinhibition, curiosity and interest, increased self-confidence and self-esteem, in a state of alert and no hallucinations or confusion. The adverse consequences can be exaggerations in the euphoria components and include disinhibition, judgment imbalance, atypical generosity, hypersexuality, repetitive compulsive actions, and extreme psychomotor agitation.^{1,4}

The agitation becomes dysphoria depending on dose and duration of consumption. It is followed by a mixture of anxiety and irritability. Anxiety ranges from mild to panic accompanied by delirium. There may be confusion in severe cases, such as in organic brain syndrome with sensory disorders. This post-cocaine dysphoria leads to repeated administration. However, the

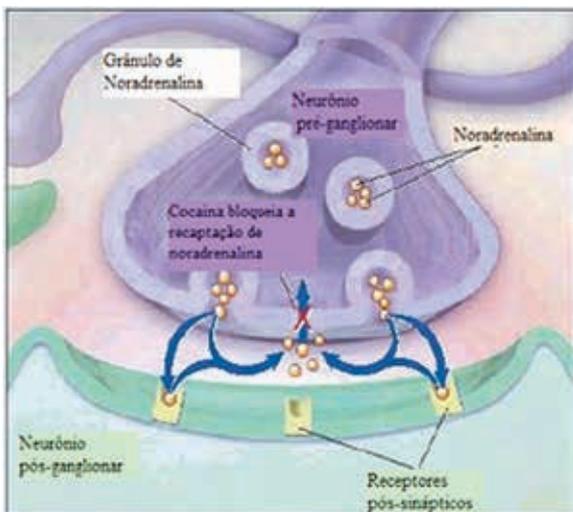


Figure 3 - Adrenergic mechanism of action of cocaine
Source: Adapted from Mosquera and Menéndez.¹

individual may be exhausted, without money, or suffer tolerance.

Consequently, a period of two phases appears: first, stimulation, and hence depression (so-called “crash”). In this, the wish to stop and rest arises and substances that facilitate sleep are sought (opioids, barbiturates, antianxiety drugs, alcohol, etc.) or a period of hypersomnia and overeating appears. Fatigue syndrome is observed in cocaine abuse after prolonged intoxication consisting of lethargy and deep sleep that can last for several hours or days followed by spontaneous recovery.^{1,4}

- **cardiovascular effects:** the heart manifests chronotropism and positive inotropism, concomitantly to the shortening of cardiac diastole that results from increased heart rate, which subsequently causes decreased heart efficiency and an increased effective refractory period of muscle fiber while shortening the transmitting time in the conductor tissue.^{1,4}

The increase in heart rate is associated with increased oxygen demand and, due to peripheral vasoconstriction, the systemic blood pressure is elevated. These two effects are mediated by the α_1 , β_1 , and β_2 receptors located in the peripheral arterial vasculature (α_1 and β_2) and the heart (β_1).^{1,4}

In the vasculature, excitatory stimulation of α_1 receptors of the coronary arteries is produced causing its constriction. In the cerebral and pulmonary arterioles, the α_2 inhibitory type receptors are stimulated causing vasodilation. These molecular actions explain the high risk of cocaine overdoses to produce acute myocardial infarction and dysfunction through mechanisms such as vasospasm and coronary occlusion by thrombus. It may be associated with acute coronary dissection after using the drug.^{1,4,6,10,11}

- **neurological effects:** the use of cocaine is associated with cerebrovascular, ischemic (45%), and bleeding events (55%). The cerebral angiography of patients who had a stroke can present stenosis or occlusion, single or multiple, and in large vessels such as the internal carotid artery. It is believed that patients with vascular malformations and cerebral aneurysms are more likely to undergo bleeding after cocaine use. Research is needed to determine whether other factors such as hypertension, smoking, alcoholism, or genetic

tendency predispose to cerebrovascular events with the use of cocaine.^{6,12}

- **effects on other systems:** in the eye, cocaine produces mydriasis due to contraction of the iris radial muscle secondary to the inhibitory stimulation of the α_1 receptor, and blurred vision secondary to relaxation of the ciliary muscle for distance vision by inhibitory stimulation through the β_2 receptor. In the urinary tract, it produces moderate urinary retention secondary to relaxation of the detrusor muscle in the bladder, and contraction of trigano and bladder sphincter. In the lungs, it produces bronchodilation, decrease in bronchial secretions, and enhanced pulmonary ventilatory capacity. In the adipose tissue, it produces stimulation of β_3 receptors causing the release of free fatty acids by lipolytic action on adipocytes. In the pancreatic islets, there is stimulation of the α_2 inhibitory and β_2 excitatory receptors producing a decrease in insulin secretion by the α_2 inhibitory effect and increased glucagon secretion by the stimulation of the β_2 excitatory receptor with increased glucose production. These effects in the pancreas result in an increase in bloodstream glucose.^{1,4}

ACUTE TOXICITY

Cocaine administered topically as a local anesthetic does not present notable systemic effects, and its action is predominantly anesthetic by stabilizing the axonal membrane and blocking peripheral nerve conduction. The real systemic action of cocaine appears with the administration by nasal, pulmonary, and parenteral routes, which quickly trigger noticeable effects in the organism.^{2,4}

The toxic dose varies widely and depends on individual tolerance, route of administration (snorted, smoked, injected), concomitant use of other drugs (alcohol, heroin, and other agents), and other factors. It produces effects in 1-2 minutes when administered intravenously. It can produce transient high levels in the brain and heart that can cause seizures or cardiac arrhythmias whereas the same dose through the nasal route can only cause euphoria. It is contemplated that blood levels of cocaine between 100 and 200 mcg% produce clinical evident alterations.^{2,4,13}

Acute complications that can lead the user to seek medical service are individual. Psychiatric

complications occur in 35.8% of cases, highlighting panic episodes, depression, and psychosis. Psychotic symptoms (paranoid delusions, hallucinations) may disappear spontaneously after a few hours (at the end of the action of cocaine), however, extreme agitation may require sedation with intramuscular benzodiazepines (midazolam 15 mg).¹²

In general, the clinical alterations produced by cocaine are presented in three phases:^{1,4,13,14}

- **Phase I. Initial Stimulation:** its primary actions are local anesthetic effects, central nervous system stimulation, and inhibition of neuronal reuptake of catecholamines. The euphoria induced by cocaine is due to a blockade of dopamine reuptake induced by the drug; however, its chronic use can cause reduced levels of dopamine and alteration in the brain dopaminergic function. This first phase is rapid (on nasal absorption it begins after 3-5 minutes of contact; in intravenous, 10-60 seconds, and in smoked; in 3-10 seconds) and is clinically characterized by euphoria, agitation, increased pulse amplitude, increased heart rate and blood pressure, headache, nausea, vomiting, dizziness, emotional instability, and involuntary movements (“ticks”) in the small muscles in the face; mydriasis occurs in the eyes. This symptomatology can be observed with blood levels above 40 mcgr%.
- **Phase II. Late or advanced stimulation:** occurs between 30 and 60 minutes after contact with cocaine, with accentuation of tachycardia, hypertension, triggering ventricular arrhythmias, difficulty breathing, irregular breathing and hyperthermia; hyperkinesia, malignant encephalopathy, tonic-clonic seizures, and status epilepticus. These clinical manifestations can be observed with cocaine blood levels between 100 and 200 mcgr%;
- **Phase III. Depression:** it is the most severe phase of acute cocaine intoxication, appearing as depression of the various systems in the body and, according to the dose ingested, occurs 1-2 hours after consumption. This phase is characterized by areflexic and unresponsive coma, fixed mydriasis, flaccid paralysis, hemodynamic instability, renal failure, ventricular fibrillation or asystole, respiratory failure, acute pulmonary edema, perioral cyanosis, thin or non-palpable pulse, decline of vital functions, unconsciousness, and death. It often occurs in suicide at-

tempts. Such symptoms are observed with levels above 3 mg per 100 mL of blood.

The diagnosis of acute toxicity is conducted by observing, in general, young adults who develop an adrenergic syndrome of short duration with psychomotor agitation, stereotyped movements, and chest pain. Complementary exams that may help define diagnosis include: CBC (frequent leukocytosis), electrolytes (attention to the levels of calcium, magnesium, and potassium because their deficiency can mimic cocaine intoxication), blood glucose (hyperglycemia), urea, and creatinine (may be elevated), blood gases, and pH (acidosis), CPK (elevated in cases of rhabdomyolysis), urine I (myoglobinuria in rhabdomyolysis), chest X-ray and electrocardiogram (in case of chest pain), CK-MB and troponin (in case of myocardial infarction), CT scan, lumbar puncture (in patients with persistent neurologic symptoms), blood cultures, and urine.¹³

Overdose is the best known acute complication related to cocaine use and is considered a medical emergency. It is characterized as a failure of one or more organs resulting from acute use and consequent increase in central and sympathetic stimulation. Its clinical symptoms are: palpitations, sweating, headache, tremors, anxiety, hyperventilation, muscle spasm, and signs of adrenergic overstimulation such as mydriasis, tachycardia, hypertension, arrhythmia, and hyperthermia. It can progress to seizures, angina pectoris with or without acute myocardial infarction, intracranial hemorrhage, and rhabdomyolysis, and death often due to heart and/or respiratory failure.¹⁴

Detoxification is a short time approach, from two to four weeks, performed in an outpatient/home care and hospital environment. This approach has been increasingly appreciated in the treatment process because it appears to increase adherence to the subsequent steps.¹⁴ In less severe cases, the cocaine intoxicating symptoms are usually of short duration and responsive to benzodiazepines in sufficient doses to normalize heart rate and blood pressure. Asymptomatic patients with normal vital signs and laboratory tests for more than 12 hours may be discharged. In moderate to severe cases, the following must be performed:

- vital respiratory and cardiovascular support;
- consider administration of benzodiazepines or barbiturates in states of agitation/seizure;

- **in hyperthermia:** establishing physical measures such as the use of cold compresses and control of room temperature;
- **in hypotension and shock:** place the patient in Trendelenburg position and administer crystalloids and vasoactive amines intravenously;
- **in rhabdomyolysis:** administration of 0.9% NaCl to maintain the urinary volume of 2-3 mL/kg/h. Monitor electrolytes, CK, and renal function. The use of diuretics and urinary alkalization might be needed.¹³

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