Vascular Toxicity of Cocaine

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Abstract: Cocaine acts on the vascular system by a number of mechanisms including monoamine re-uptake inhibition, local anesthesia, anti-cholinergic activity, alpha-adrenergic stimulation, regulation of various vasoconstrictor and vasodilator agents and promotion of prothrombotic state. These effects lead to a number of clinical syndromes *via* vasoconstriction, platelet activation, thrombus formation and early atherosclerosis in almost every organ of the body. Many of these effects may be under appreciated. Furthermore, cocaine is commonly associated with the use of tobacco and alcohol which can lead to superadditive effects and/or prolonged toxicity.

Keywords: Cocaine, vasoconstriction, platelet activation, atherosclerosis, infarction, cocaethylene, alcohol, nicotine.

INTRODUCTION

The cocoa plant (Erythroxylon coca) has been used of for centuries for its stimulant, euphorigenic and medicinal properties. The earliest records of its use, dates back to the ancient people of Peru and pre-Colombian Andean societies [1, 2].

In the 19th century there were no laws regulating the sale of cocaine and therefore it was widely available. Coca cola and a number of other beverage manufacturers mixed cocaine in their drinks [1]. A number of prominent people are known to have used cocaine, including Sir Arthur Conan Doyle, Sigmund Freud and former US president Ulysses S. Grant [3].

The United Nations Office on Drugs and Crime (UNODC) estimated that 14 million people worldwide or 0.3% of the population aged 15 – 64 used cocaine in 2005. The largest number of cocaine users are in North America (6.4 million) followed by western and central Europe (3.9 million) and South America (including Central America and Caribbean: 2.2 million) (UNODC World Drug Report 2007, www.unodc.org). Currently cocaine is one of the most common illicit drugs used in North America (2005 National Survey on Drug Use & Health, www.oas.samhsa.gov/nsduh).

PHARMACOLOGY

Cocaine is an alkaloid extracted from the leaves of the Erythroxylon plant. This alkaloid is modified into various forms for consumption, the most common of which are crack and cocaine hydrochloride [4].

Cocaine is absorbed through mucous membranes and can therefore be snorted, inhaled, smoked or injected [5]. The time to reach peak plasma concentration depends on the method of consumption [4, 6], which is summarized in Table **1**.

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Nasal inhalation of cocaine delays the time to reach peak plasma concentration because of vasoconstriction of intranasal blood vessels. This leads to delayed and longer lasting euphorigenic effects than achieved with other routes of cocaine administration [4, 6].

Cocaine has a short half-life in plasma of about 30 to 90 min [4, 6]. It is metabolized to methyl esters and benzoylecgonine by the liver and eliminated by the kidneys. Benzoylecgonine can be detected in urine 1-2 weeks after ingestion of cocaine. A small amount of cocaine is not metabolized and cleared as such by the kidney and, is detectable in urine for 4-6 h after consumption [4-7].

Major Modes of Action:

1) Monoamine re-uptake inhibitor: Responsible for sympathomimetic actions in the peripheral nervous system by inhibiting the re-uptake of catecholamines in presynaptic nerve terminals [8-12] and euphorigenic effects by inhibiting re-uptake of dopamine and serotonin in the central nervous system [13-15].

2) Local anesthesia: Cocaine competitively inhibits sodium channels in electrically active cells such as neurons and myocardium. This delays nerve conduction and thus decreases the ability to transmit impulses [16-19].

3) Anticholinergic action: Cocaine can inhibit muscarinic receptors in the heart [20, 21] and brain [22, 23]. This action requires the concentration of cocaine to be about 20 times higher than that required to produce euphoria [24]. This concentration is generally not reached by inhalation or smoking. Anticholinergic toxicity of cocaine is seen in body packers when the ingested cocaine packets rupture, releasing large amounts of cocaine [25-27].

Cocaine has a number of other actions by which it may lead to toxic effects including alpha adrenergic stimulation [28, 29], increase in endothelin [30] and decrease in nitric oxide production [31].

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Table 1. Forms of Cocaine and Time to Reach Peak Plasma Concentration

Forms of Cocaine	Method of Consumption	Onset of Action	Peak Effect	Duration of Action
Freebase (Crack)	Inhalation (Smoking)	3 - 5 sec	1 -3 min	5 - 15 min
Cocaine hydrochloride	Intravenous	10 - 60 sec	3 - 5 min	20 - 60 min
	Intranasal (or other mucosal)	1 - 5 min	15 - 20 min	60 - 90 min

VASCULAR EFFECTS OF COCAINE

1. Effect on Vascular Resistance

Inhalation of cocaine leads to an early phase of vasodilatation followed by vasoconstriction [32]. The early vasodilatory action is attributed to its local anesthetic effect [33].

The generalized vasoconstrictor response is multifactorial and may be due to inhibition of neuronal re-uptake of catecholamines which leads to super-sensitivity to endogenous and exogenous norepinephrine. We have shown that the contractile response of ferret muscles is inhibited when they are pretreated with reserpine (Fig. (**1**)) [34]. This happens because reserpine depletes the synaptic vesicles of norepinephrine. Therefore, after cocaine administration, norepinephrine levels do not increase in the synaptic cleft leading to a blunted vasoconstrictor response.

Excess neurotransmitters in the alpha adrenergic [28, 29] and muscarinic nerve [35] endings mediate contraction of the blood vessels. Our experiments on porcine coronary artery demonstrate that the decrease in arterial diameter with co-administration of cocaine and prazosin (alpha receptor antagonist) is blunted [35]. Interestingly in the same experiment when we co-administered cocaine with atropine (anticholinergic agent) the vasoconstrictor response was inhibited much more than with prazosin (Fig. (**2**)). Therefore, we concluded that potentiation of both alpha adrenergic and muscarinic (M3 subtype) receptors are responsible for vasoconstrictive action of cocaine with the muscarinic pathway playing a greater role, especially in the coronary arterioles with a diameter of less than 200 micrometers, which are populated with the M3 receptor subtype [35].

Cocaine also produces vasoconstriction by increasing the production of endothelin-1 *via* stimulation of endothelial sigma receptors [30] and decreasing nitric oxide synthesis by the endothelial cells [31].

Chronic cocaine use reduces relaxation of vascular beds especially in the coronary micro-vasculation *via* down regulation of beta-adrenergic receptors and also by reduction of endothelium–dependent relaxation to serotonin [35].

The clinico-pathologic effects mediated by cocaine induced vasoconstriction include myocardial infarction [36, 37], stroke [38-40], mesenteric ischemia [41], renal infarction [42], gastric and duodenal ulceration and perforation [43].

2. Effects on Platelets and Thrombus Formation

Cocaine use is associated with enhanced platelet activation and aggregability, [44, 45] which may lead to thrombus

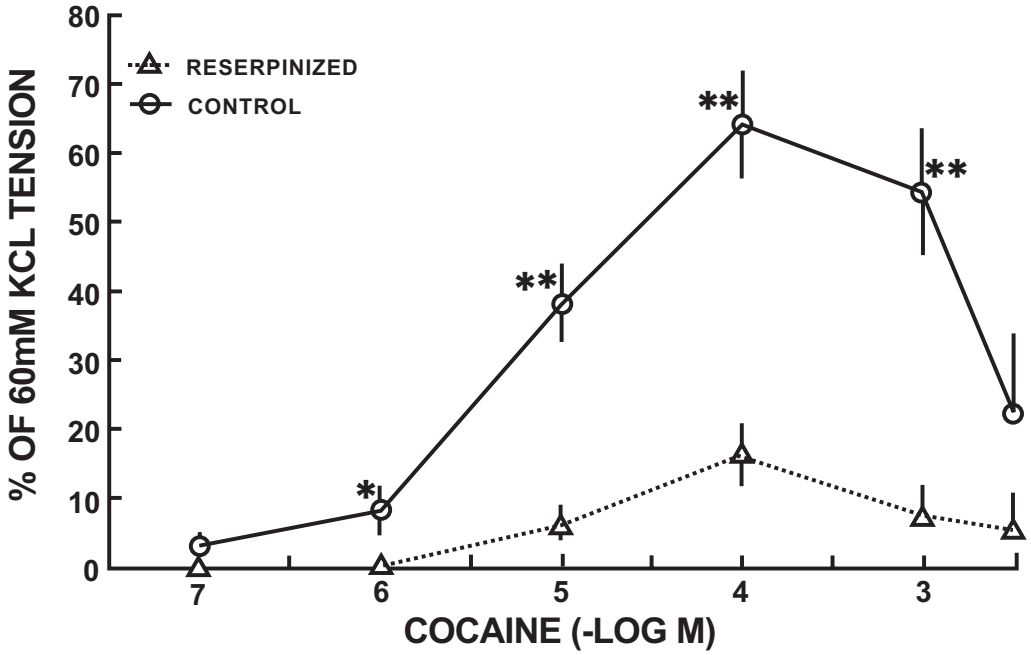

Fig. (1). Dose response relationship in control muscles and muscles pre-treated with reserpine.

formation [46]. The demonstration of platelet rich thrombi in coronary arteries of patients undergoing fatal myocardial infarction gives credence to this theory [47]. Besides the coronary arteries, cocaine-mediated thrombosis has also been observed in the pulmonary [48], skin [49], peripheral [50] renal [42] and cerebral circulation [38-40].

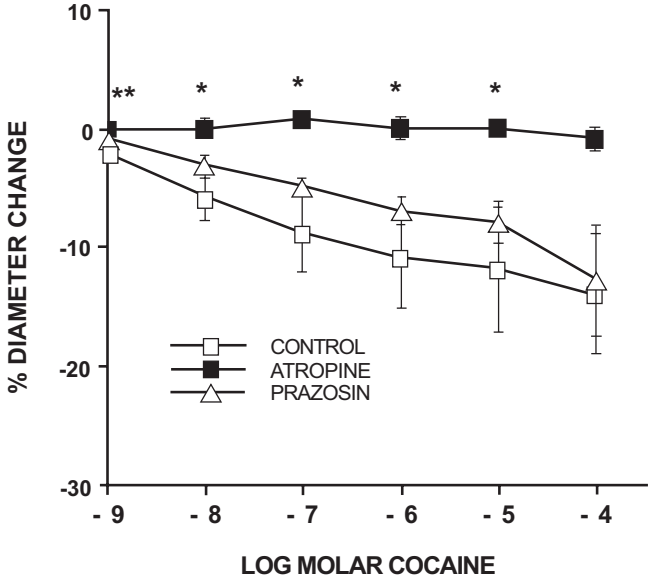

Fig. (2). Action of cocaine on porcine coronary microvessels with effect of co-administration of atropine (anticholinergic) and prazosin (alpha adrenergic antagonist).

The mechanism by which cocaine causes platelet activation is not clear. Cocaine induces the expression of P-selectin [51], release of alpha granule contents [44] and binding of fibrinogen to the platelet surface [44]. It may also enhance the degree of activation induced by other agonists, such as epinephrine, when present in sub-threshold concentrations [44].

Recently, Heesch *et al.* demonstrated that intranasal administration of cocaine (2 mg/kg) to drug naive healthy human volunteers led to platelet activation, alpha granule release, formation of platelet microaggregates and a slight decrease in bleeding time [52].

Besides platelet activation, cocaine also increases the plasma concentration of tissue plasminogen activator inhibitor [53], von Willibrand factor [54], blood viscosity (by increasing red blood cells) [54] and tissue factor levels [55]. There is a concomitant decrease in tissue factor pathway inhibitor [55]. These effects favor a prothrombotic state.

3. VASCULAR INJURY AND ATHEROSCLEROSIS

Cocaine can cause direct and indirect vascular injury leading to premature atherosclerosis [56, 57], aneurysmal dilatation [56] and aortic dissection [58].

Direct vascular injury may be mediated by increasing endothelial permeability to LDL [59], enhancing the expression of endothelial adhesion molecules leading to leukocyte migration [60] and proliferation of adventitial mast cells [57].

Indirect vascular injury may be mediated by cocaine-induced platelet activation that releases platelet-derived mitogens, including platelet-derived growth factor, epidermal growth factor, and transforming growth factor-beta, from platelet alpha-granules that may contribute to premature atherosclerosis [57, 61].

Cocaine has been shown to induce apoptosis in rat aortic smooth vascular cells [62] and human coronary artery endothelial cells [63]. These factors may also play a role in early atherosclerosis, weakening of vessel wall and formation of aneurysms. Hypertension due to cocaine use [32] may then lead to arterial dissection [58] and aneurysmal rupture [39, 56, 64].

Cocaine and Ethanol

Concurrent use of cocaine and alcohol leads to formation of cocaethylene, a metabolite synthesized by transesterification in the liver [65]. In animals, cocaethylene has been shown to be more toxic than cocaine [66, 67]. Cocaethylene shares the same molecular targets as cocaine [68] and because of its prolonged half life (cocaethylene, 2 – 4 h *vs.* cocaine which is 30 – 90 min) it may lead to persistent toxicity [69, 70]. Cocaethylene inhibits the re-uptake of dopamine at the synaptic cleft [66, 68] and enhances microvascular permeability [71]. Our experiments demonstrated that cocaethylene is 10-fold more potent than cocaine in decreasing peak intracellular calcium and myofilament responsiveness in ferret cardiac muscles to produce a negative inotropic effect [67].

Since humans are unable to distinguish the effect of cocaethylene from cocaine [72] it is speculated that in some cases the delayed toxicity caused by cocaine can be attributed to cocaethylene [73-77].

Cocaine and Nicotine

Cocaine consumption is commonly associated with cigarette smoking, alcohol and marijuana use [78]. People using tobacco, alcohol and marijuana have a 75% chance to try cocaine by a median age of 17 years [78]. Within minutes of cigarette smoking, nicotinic receptors in the adrenal medulla are stimulated, triggering the release of norepinephrine and epinephrine [79]. Nicotine has been shown to increase myocardial oxygen demand [80, 81] and cause vasoconstriction in angiographically normal and diseased segments of coronary arteries [82, 83]. Nicotine-induced vasoconstriction may be attributed to multiple mechanisms: 1) Potentiation of alpha adrenergic receptors similar to cocaine [84], 2) Injury to endothelial cells [85], and, 3) Reduction of prostacyclin formation [86, 87]. Therefore, the harmful effects of cocaine on myocardial oxygen supply and demand can be substantially exacerbated by cigarette smoking leading to an increased probability of acute coronary syndromes and ischemia in other organs.

CONCLUSIONS

Cocaine remains the most commonly abused drug responsible for emergency department visits to the hospital

(Drug Abuse Warning Network (DAWN) Report – Oct 2002, www.oas.samhsa.gov). It causes a number of clinical syndromes due to its varied vascular insults including vasoconstriction, platelet activation and aggregation, thrombus formation and early atherosclerosis. The most common sequelae recognized is myocardial infarction. However, other clinical entities (Table **2**) may be commonly missed or when recognized may not be attributed to cocaine use. The understanding of pathophysiologic mechanisms causing vascular toxicity in cocaine abusers is essential for the correct diagnoses, treatment and prevention of potentially lethal outcomes.

Table 2. Common Vascular Complications Caused by Cocaine Use and their Mechanism

Clinical Syndrome	Mechanism
Myocardial Infarction [36, 37] Ischemic stroke [38-40] Mesenteric Ischemia [41] Renal infarction [42] Pulmonary Infarction [48]	Vasoconstriction Platelet activation Thrombus formation Atherosclerosis Plaque disruption
Intracranial hemorrhage [39, 64] Aortic Dissection [56, 58]	Hypertension Aneurysm formation Disruption of vascular muscle fibers
Gastric and duodenal ulceration/perforation [43]	Vasoconstriction Delayed gastric emptying *via* cholinergic activation leading to increased exposure to hydrochloric acid
Nasal septal perforation [88] Oropharyngeal ulcers [89]	Vasoconstriction of local blood vessels (due to inhalation or snorting cocaine)
Pulmonary interstitial and alveolar hemorrhage [90] Pulmonary edema [91, 92]	Direct vascular toxicity Increased microvascular permeability Increased pulmonary capillary pressure Increased systemic vascular resistance
Rhabdomyolysis [93, 94] Acute renal failure [93, 94]	Vasoconstriction of intramuscular arteries Direct toxic effect Tonic clonic seizures
Spontaneous abortion [95] Abruptio placentae [96] Prematurity, Intra-uterine growth restriction [97]	Vasoconstriction of placental vessels Maternal hypertension

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