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Cocaine and the heart.

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Introduction

Cocaine is currently the second most commonly used illicit drug in the United States, with marijuana usage being the commonest (1). Its use had reached epidemic proportions in the mid-1980s after which there was a decline in its prevalence. There has, however, been a resurgence in its usage and between 1994 and 1998 when the number of new cocaine users per year increased by 82% (1,2). According to the 1998 National Household Survey on Drug Abuse (NHDSA) approximately 11% of the population of the United States has used cocaine at some point in their lifetime, most frequently by males between the ages of 18 and 25 years (3).

Cocaine may be associated with either acute or chronic toxicity, and approximately 5-10% of emergency department visits in the United States are believed to be secondary to cocaine usage (4). Chest pain is the most common cocaine-related medical problem, leading to the evaluation of approximately 64,000 patients annually for possible myocardial infarction. Fifty seven percent of these are admitted to hospital, resulting in an annual cost greater than \$83 million (5). There is a plethora of cocaine-related cardiovascular complications, including acute myocardial ischemia and infarction, myocarditis, arrhythmias and sudden death, myocarditis and cardiomyopathy, hypertension and aortic rupture, and endocarditis (6-12). There is no evidence to suggest that preexisting cardiovascular disease is a prerequisite for the development of a cocaine-related cardiovascular event, although it may be a potentiating factor, as may be nicotine and alcohol (13,14). The aim of this paper is to discuss our current understanding of the potent effect of cocaine on the cardiovascular system and currently available therapeutic options.

Pharmacology

Cocaine (benzoylecgonine, $C_{17}H_{21}NO_4$) is an alkaloid derived from the leaves of the *Erythroxylon coca*, a plant that is native to South America. It was first used as a local anaesthetic in 1884 and, interestingly, was used as an ingredient in the Coca-Cola beverage in the early 20th century (15). The crystalline (powder) form of cocaine is prepared by dissolving this alkaloid in hydrochloric acid that forms the water-soluble salt, cocaine hydrochloride. The freebase cocaine or “crack” (due to the crackling sound made when the crystals are heated) is the alkaloid in a basic non-salt form, prepared from cocaine hydrochloride by an organic extraction from a basic solution with ether (16).

Cocaine is absorbed from all body mucous membranes and can be administered by sublingual, intramuscular, intravenous and respiratory routes. The onset of action varies from 3 seconds to 5 minutes depending on route of administration. Also dependent on route of administration are the peak effects and duration of action, which vary from 1 to 20 minutes and 5 to 90 minutes, respectively. In humans cocaine has an elimination half-life of 30 to 60 minutes and is metabolized by plasma and hepatic cholinesterases to water soluble compounds which are excreted in the urine (17). Approximately 5-10% of total cocaine dose is excreted unchanged in urine. Unmetabolized cocaine is usually not present in serum after 6 hours, but the metabolites can be detected for up to 48 hours and benzoylecgonine has actually been detected in urine as long as 22 days after the last dose of cocaine in asymptomatic patients with histories of significant cocaine abuse (17,18). This may have important clinical implications, such as establishing a correct diagnosis of possible myocardial damage in the emergency room secondary to recent cocaine abuse.

Cocaine is a central nervous system stimulant affecting the release and reuptake of serotonin and dopamine in the brain. It blocks the re-uptake of norepinephrine and dopamine at preganglionic synaptic nerve endings, increasing the synaptic concentrations of these monoamines and enhancing the effect of norepinephrine. Cocaine can cause the release of norepinephrine and epinephrine from the adrenal medulla (19,20). It also has unusual pharmacological effects as it can inhibit the initiation or conduction of nerve impulses, resulting in its anaesthetic effect. Cocaine can also cause central and peripheral vasoconstriction.

Myocardial Ischemia and Infarction

The cardiac effects of cocaine are complex. While there is increased adrenergic activity increasing myocardial contractility and conduction, there is also a local anaesthetic effect depressing myocardial function. It is believed that cocaine induced alterations in calcium availability may play a vital role in its ability to directly affect the myocardium and vasculature. The net result appears to be an increase in sympathomimetic activity, resulting in increased myocardial contractility, heart rate, blood pressure and increased myocardial oxygen demand (21,22).

There is a 24 fold increased risk of acute myocardial infarction during the initial 60 minutes after the use of cocaine in patients who are otherwise at low risk (23). The pathogenesis of cocaine-induced myocardial infarction in patients with normal coronary arteries may involve focal occlusive vasospasm and endothelial dysfunction, diffuse coronary vasoconstriction, as well as coronary thrombosis (24). Of note, premature

coronary atherosclerosis has been seen in young cocaine abusers, with obstructive coronary artery disease seen in 35-40% of patients who undergo angiography for cocaine associated chest pain (34).

Experimental evidence suggests cocaine alters the integrity of vascular endothelium by reducing prostacyclin production, thereby reducing vasodilation (reference). Endothelial dysfunction associated with early atherosclerosis has been shown to result in hypersensitivity to the vasoconstrictor effects of cocaine-induced catecholamine release (reference). Cocaine may also directly enhance platelet aggregation and potentiate platelet thromboxane production (25,26,27). The administration of intranasally administered cocaine is associated with an increase in plasma plasminogen activator inhibitor, which could potentiate vascular thrombosis.

While focal coronary vasospasm has been postulated as a primary cause of cocaine-induced myocardial infarction, it has been angiographically documented in only two patients with normal coronary arteries (28,29). Damage to the endothelium at the site of focal arterial constriction may serve as a nidus for platelet adhesion resulting in coronary thrombosis (33). Cocaine may directly enhance platelet aggregation or increase platelet aggregation through alpha-adrenergic mediated mechanisms (27).

Cocaine causes the release of norepinephrine from adrenergic nerve terminals which has been shown to cause diffuse coronary vasoconstriction of normal human epicardial coronaries both in-vitro and in-vivo (reference). Two studies have shown that administration of intranasal cocaine results in a significant reduction of coronary diameter as measured by quantitative coronary angiographic analysis (reference). In neither study, however, was there any angina or electrocardiographic evidence of myocardial ischemia (30,31,32).

Cardiomyopathy and Myocarditis

Cocaine may depress left ventricular function in the absence of acute coronary ischemia. Cocaine has a direct negative inotropic effect on cardiac muscle (35). Clinical studies have demonstrated cocaine to be associated with transient left ventricular dilatation and decreased ejection fraction. This is often referred to as transient toxic cardiomyopathy associated with cocaine use, similar to catecholamine cardiomyopathy of pheochromocytoma (36,37). Possible explanations include excess catecholamines leading to cell damage due to calcium overload of myocytes or by transient vasoconstriction of coronary vessels and subsequent myocyte death. There is still debate as to whether the appearance of a mononuclear cell infiltrate is a secondary reaction to myocyte death or whether it represents a primary hypersensitivity reaction to cocaine, with a resultant myocarditis (38).

Cocaine-induced arrhythmias

Cocaine exhibits sodium-channel blocking abilities, thus prolonging the duration of the QRS and QT intervals. When coupled with its ability to produce an enhanced

sympathetic state, can induce arrhythmias (39). Cocaine also reduces vagal activity, is a sympathomimetic agent increasing myocyte irritability, and increases intracellular calcium which can produce afterdepolarisations and triggered ventricular arrhythmias. The cocaine-associated long QTc interval is possibly related to the effects of cocaine and its metabolites on the conduction in the Human Ether-a-go-go Related Gene (HERG)-encoded potassium channel (40,41). Cocaine has also been reported to produce a transient Brugada-type electrocardiographic pattern, the clinical importance of which is not known (42). It is important to note that studies in animals and humans have shown that cocaine precipitates ventricular arrhythmias and fibrillation mainly in the presence of myocardial ischemia, infarction or in those with non-ischemic myocellular damage (43).

Endocarditis

Cocaine, when administered intravenously, has been associated with endocarditis, primarily left-sided. The mechanism is unclear but thought to be immune mediated or secondary to contaminants often present in cocaine. The cocaine-mediated increased heart rate and systemic blood pressure may predispose valves to injury, promoting bacterial infection (12).

Polysubstance abuse

Cocaine ingested concomitantly with alcohol or cigarettes is more lethal than the adrenergically-mediated effects of cocaine alone. Cigarette smoking increases the myocardial oxygen requirements while decreasing coronary diameter, exacerbating cocaine cardiotoxic effects. Cocaine and alcohol undergo transesterification in the liver resulting in the metabolite cocaethylene. This metabolite blocks dopamine re-uptake, increasing dopamine concentrations in the synaptic gaps, and exacerbating the effects of cocaine on heart rate and blood pressure (40).

Diagnosis

Diagnosing myocardial ischemia in a patient post-cocaine ingestion can be difficult in the emergency room. Current literature suggests that up to 84% of patients with cocaine-related chest pain can have abnormal ECG's. Yet, as many as 43% of cocaine users with no myocardial infarction can have significant ST segment elevations. Conversely, a relatively normal appearing ECG may not be sufficient to rule out an MI (5,44).

The specificity of myoglobin as a marker of acute myocardial infarction is altered by recent cocaine use. However, the specificity of CK-MB is affected less and that of cardiac troponin I is not affected by recent cocaine use (45). Because of the difficulty in being able to accurately assess patients with chest pain and recent cocaine usage, most emergency departments routinely admit such patients for monitoring.

Treatment

According to the American College of Cardiology/American Heart Association (ACC/AHA) task force guidelines, the initial mainstays of treatment in cocaine induce coronary ischemia include aspirin, nitrates and benzodiazepines. If there is persistence of chest pain, the addition of calcium channel blockers and alpha blockers may be considered, since cocaine induced coronary vasoconstriction is largely secondary to

alpha-adrenergic stimulation. In the case of the diagnosis of an acute MI, the patient should be triaged appropriately for possible cardiac catheterization or thrombolysis as per AHA/ACC guidelines. Lidocaine may be used as an antiarrhythmic agent during the peri-infarction period, but should be used with caution due to the possible additive proarrhythmic complications of these drugs when combined with the proarrhythmic properties of cocaine (46).

The issue of a beta-blocker contraindication in patients with cocaine-induced chest pain has never been, and is unlikely, to be fully resolved. Cocaine is associated with coronary artery vasospasm due to both direct smooth muscle stimulation and alpha-stimulation. There is the concern that beta-blockers would impede beta-adrenergic mediated vasodilatation. However, beta-blockade may be beneficial against the pathophysiologic effects of cocaine in the peri-myocardial infarct period, including systolic dysfunction heart failure, coronary artery thrombotic occlusion and ventricular arrhythmias. A recent retrospective cohort study concluded that the administration of beta-blockers was associated with a reduction in the incidence of myocardial infarction after cocaine use and that the benefit of beta-blockers on myocardial function may offset the risk of coronary artery vasospasm (47).

Conclusion

Cocaine-induced chest pain in a younger population group is a common presentation in emergency departments across the United States. This is largely due to the hyperadrenergic state and pro-thrombotic properties of cocaine. Cocaine may induce life threatening arrhythmias and increase the risk for endocarditis. Due to its often covert presentation in the acute setting most patients presenting with cocaine-associated chest pain are admitted for at least 24-hour monitoring. Therapy is largely based on administration of supplemental oxygen, aspirin, nitrates and benzodiazepines if patients are tachycardic, hypertensive or anxious. The role of beta blockers in the setting of a cocaine-induced myocardial infarction remains controversial. The management of cocaine-induced acute myocardial infarction should be according to current ACC/AHA guidelines. Ultimately, the goal should be to encourage abstinence from this lethal drug.

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