International Journal of Cardiology 277 (2019) 198–199

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Editorial

Beta-blockers: A real antidote for cocaine-related heart disease?☆

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ARTICLE INFO

Article history:
Received 26 September 2018
Accepted 1 October 2018
Available online 3 October 2018

Keywords:
Cocaine
Heart failure
Beta-blockers

"The first time I took 0.05cg. of cocaïnum muriaticum in a 1% water solution was when I was feeling slightly out of sorts from fatigue. A few minutes after taking cocaine, one experiences a sudden exhilaration and feeling of lightness."
[[Freud S, Über Coca, Centralblatt für die ges. Therapie, 2, pp. 289–314, 1884]]

Cocaine is the second most widespread illicit drug in Europe, after cannabis, estimated to be used by around 13 million Europeans at least once in their lifetime (3.9% of adults aged 15–64 years) [1]. Cocaine can be smoked, snorted, absorbed through all mucosae or administered intravenously, with different pharmacokinetics (the onset of action varying from 3 s to 5 min, the effect lasting for 30 min after intravenous administration to three hours after ingestion). Cocaine increases the activity of monoamine neurotransmitters in the central and peripheral nervous system, blocking the reuptake of dopamine, norepinephrine and serotonin, and modulates endogenous opioid receptors leading to a sensation of increased energy, alertness, euphoria and decreased tiredness [2]. It is hydrolysed in the liver by carboxyesterases into water-soluble compounds which are excreted in the urine: other substances, such as alcohol and opioids, can interfere with its metabolism and increase its effects.

Cocaine use is associated with acute and chronic complications that may involve any system, the most common being the cardiovascular system. It has been estimated that a quarter of non-fatal myocardial infarctions in people aged 18–45 years are attributable to cocaine use [1]. The pathophysiology of cardiovascular complications involves several mechanisms [2]: besides sympathetic-mediated effects (coronary and peripheral vasoconstriction, as well cardiac inotropism and chronotropism), cocaine acts directly on endothelial cells by blocking nitric oxide (NO) synthase and promoting endothelin-1 release, on vascular smooth muscle cells by impairing acetylcholine- induced vasorelaxation and intracellular calcium handling, but also on cardiomyocytes, by directly blocking sodium, potassium and calcium channels, with direct negative inotropic and pro-arrhythmic effects similarly to other sodium channel blockers. During concomitant cocaine and alcohol assumption, a cardiotoxic metabolite (cocaethylene) is also produced. Furthermore, cocaine induces a proinflammatory and prothrombotic state by activating mast cells, platelets (directly or inhibiting platelet reuptake of serotonin) and coagulation (increasing endothelial tissue factor, fibrinogen and plasminogen activator inhibitor-1).

On the one hand, all these mechanisms cause increased myocardial oxygen demand, vasospasm and thrombosis in the acute setting, but also early-onset atherosclerosis with iterative use, leading to acute coronary syndromes and chronic ischaemic cardiomyopathy. On the other hand, non ischaemic cardiovascular complications of cocaine use comprise hypertensive crises, aortic dissection or rupture, cerebral haemorrhage, kidney mesangial fibrosis, arrhythmias and sudden cardiac death, endocarditis, Takotsubo syndrome, myocarditis, cardiac hypertrophy, dilated cardiomyopathy and heart failure [2].

Besides ischaemic changes, cardiac histological findings comprise loss of myofibrils, hypercontracted myofilaments, contraction band necrosis, interstitial infiltrates with inflammatory cells and fibrosis; in some cases, myocarditis characterized by perivascular eosinophilic infiltrates has been attributed to a hypersensitivity reaction to cocaine or contaminants, such as amphetamine, sugars or talc. Endocarditis is promoted by injected bacteria, but also by immune dysregulation and predisposing histological tissue lesions. Vascular abnormalities include endothelial dysfunction, smooth muscle cells apoptosis and cystic medial necrosis. Several cardiovascular magnetic resonance studies

☆ The authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.
DOI of original article: https://doi.org/10.1016/j.ijcard.2018.08.058.

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https://doi.org/10.1016/j.ijcard.2018.10.003

confirm the presence of myocardial oedema in up to 47% and fibrosis in up to 73% of asymptomatic cocaine users [3,4].

Beta-blockers are a cornerstone of cardiovascular therapy, but their use in cocaine addicted patients has been debated, since a case report in 1985 [5] suggesting that selective beta-blockers might produce not only a paradoxical hypertension as a result of unopposed α-receptor stimulation, but also coronary artery vasoconstriction. Another case report described cardiovascular collapse and death in a patient treated with metoprolol after consuming 1 g of intranasal cocaine [6]. For this reason, the β1/β2/α1-blocker labetalol was used in patients who were initially treated with intranasal cocaine [7], and although labetalol did not worsen the cocaine-induced coronary vasoconstriction, its lack of effect further contributed to the growing perception of the inappropriateness of beta-blocker therapy in cocaine users. Recent studies on cocaine addicted patients treated with beta-blockers have been published and generally showed neutral or even beneficial effects on cardiovascular outcomes [8,9].

In this issue of the Journal, Lopez et al [10] performed a retrospective analysis on 72 beta-blocker-naïve active cocaine users, affected by heart failure with reduced ejection fraction (HFrEF). After 12 months of treatment, 38 patients receiving beta-blockers were more likely to have an improvement in their New York Heart Association functional class (NYHA) and left ventricular ejection fraction (LVEF), as well as lower cardiovascular events and heart failure hospitalizations, compared with 34 patients not receiving beta-antagonists. When comparing patients who received mixed alpha/beta blockade (carvedilol, n = 23) with those who received β1-selective blockade (metoprolol succinate, n = 15), there was no difference in LVEF improvement, while NYHA class showed a larger improvement in the carvedilol subgroup. The small number of patients and the retrospective nature of the study represent major limitations, particularly because beta-blockers were not randomly prescribed, nor was a correction with propensity score matching performed, so that a "treatment bias" might be present. Moreover, information about therapy adherence was lacking, as well as about the amount and route of cocaine use: this is a crucial point for all studies on illicit drug assumption. On the one hand, all patients should be regularly and frequently evaluated during follow-up, in order to guarantee therapeutic adherence during the study; on the other hand, the exclusion of less compliant patients from the study represents a referral bias, making the study significantly less representative of the general patient population. Finally, the pathological substrate of HF was not fully investigated: coronary angiography was performed in the majority (n = 52, 72%) but not all patients; nor was cardiovascular magnetic resonance performed, to investigate the presence and extent of myocardial fibrosis and oedema. Overall, the study by Lopez suggests that betablocker therapy is generally safe and effective in cocaine addicts with HFrEF, but their results are not conclusive. Further multi-centre studies are needed to investigate the best preventive and treatment strategies in cocaine users.

Conflicts of interest

None.

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