A Fatal Drug Interaction

S. Eliza Halcomb MD
Lewis Nelson MD
New York City Poison Control Center.

A 54-year-old man was brought into the emergency department complaining of crushing substernal chest pain after using cocaine earlier that morning. The pain was of sudden onset, lasting for three hours, aggravated by exertion and relieved by rest. His past medical history was significant for hypertension. He denied taking any medications and had no known drug allergies. His social history was remarkable for a 30-pack year smoking habit and frequent cocaine use.

On examination, he was alert and oriented sitting up in bed. His blood pressure was 145/95 mmHg, heart rate was 115/min, breathing at 20/min and he was afebrile with a temperature of 96.8°F. His cardiovascular exam was notable for tachycardia and jugular venous distension. His lungs were clear to auscultation bilaterally, with no notable wheezes or crackles. His abdominal and neurologic exams were normal. An electrocardiogram showed a sinus tachycardia, and was otherwise normal.

What are the initial steps to take in the care of this patient?

The symptoms described by this patient are concerning for an acute coronary syndrome such as unstable angina or myocardial infarction. The initial management, particularly in this patient experiencing subjective breathing difficulties, should include assurance of adequate gas exchange (airway and breathing), as well as circulation. These issues each need to be addressed to minimize damage to ischemic cardiac muscle. The initial interventions in this case included placing the patient on oxygen, inserting an intravenous catheter and attaching the patient to a cardiac monitor. He then had an ECG done and labs sent. Other causes of chest pain should be considered and appropriately evaluated.

What else should this patient receive?

All patients presenting with chest pain believed to be of cardiac origin should receive an aspirin and nitroglycerin, unless contraindicated. Aspirin has anti-platelet effects that prevent clot formation and nitroglycerin has vasodilatory effects that help increase blood flow to potentially ischemic myocardium. Cocaine causes platelet stickiness that may enhance thrombus formation, so aspirin has therapeutic value. Intravenous morphine alleviates the perception of chest pain, and in this case reduces the psychomotor agitation, which by reducing the patient's sympathetic tone, decreases the adverse hemodynamic effects. Although improving blood flow to the heart is paramount, a critical corollary intervention includes reducing the oxygen requirement of the heart.

What are the concerns about using the traditional pharmacologic agents in the setting of cocaine use?

Beta-adrenergic antagonists alleviate the patient's tachycardia by preventing the binding of endogenous catecholamines on the cardiac β-1 adrenergic receptors. Blockade of these receptors has both negative ionotropic and chronotropic effects leading to reduction of cardiac work and oxygen consumption as well as a reduction in the mean arterial blood pressure. Note that because there are β-2 receptors on the skeletal muscle vasculature, the use of non-selective β-adrenergic antagonists does not typically result in a precipitous fall in mean arterial blood pressure. That is, since stimulation at these receptors produces vasorelaxation, mild peripheral vasoconstriction may occur through their antagonism.

This patient had used cocaine on the day of presentation. Cocaine is a centrally acting sympathomimetic agent. Its mechanism of action is to prevent the reuptake of norepinephrine and other biogenic amines at nerve endings, which, among other things, increases the outflow of activity via the peripheral sympathetic nerves. Alpha-adrenergic receptor stimulation is prominent from the peripherally-released norepinephrine in patients with high sympathetic tone, resulting in vasoconstriction and hypertension.

Given its central nervous system site of action, the most effective way to treat the clinical manifestations of cocaine is with sedation, typically with benzodiazepines. By decreasing central nervous system activity, there is a concomitant reduction in peripheral sympathetic outflow. If this does not produce sufficient hemodynamic control, vasodilators such as nitroprusside, or preferentially phentolamine, an α-adrenergic antagonists, may be useful.

There are major concerns about using β-adrenergic antagonists to reduce the heart rate or blood pressure in patients with cocaine-related ischemia. Since cocaine causes α-mediated vasoconstriction, β-adrenergic antagonism may block β-2 mediated vasodilation. Thus, the concomitant use of β-adrenergic antagonists may result in life-threatening hypertension and associated complications as a result of “unopposed alpha” vasoconstriction. That is, since cocaine causes its peripheral hemodynamic effects through the release of norepinephrine from the sympathetic nervous system and since norepinephrine has a potent α-adrenergic agonist effect, the use of non-selective (and probably all) β-adrenergic antagonists eliminate the small amount of β-2 mediated vasodilatation. Thus, the α-adrenergic effects remain and produce unopposed vasoconstriction. A 1990 study by Lange et al. found that administration of propranolol in the setting of low dose cocaine use resulted in increased coronary vascular resistance and a reduction in the diameter of the coronary artery. A 1993 study by Boehrer et al

showed that labetolol administration in the setting of low dose cocaine use caused an increase in mean arterial blood pressure, no change in heart rate and a decrease in coronary artery area, and clearly demonstrated coronary artery vasoconstriction angiographically. That is, labetolol, despite is α-adrenergic antagonistic effects, is no better than propranolol.

Case Continuation

This patient's pain was completely relieved with the administration of aspirin, however he remained tachycardic and hypertensive, which concerned the clinician due to the aforementioned increase in oxygen consumption. Thus, a decision was made to use benzodiazepines to treat his heart rate and blood pressure. However, this patient's heart rate and blood pressure remained slightly elevated one hour after his arrival to the emergency department (about 6 hours after his cocaine use). A decision was made to administer intravenously a low dose (2.5 mg) of metoprolol. This lowered the systolic blood pressure to 125 mmHg and his heart rate dropped from 115 to 105. Another 2.5 mg metoprolol was administered minutes later, after which the patient immediately complained of severe chest pain, vomited and collapsed. CPR was commenced with no return of spontaneous circulation.

Why did this occur?

This was an unfortunate case in that the physician felt that since the patient had used cocaine 6 hours prior to arrival; it was probably safe to treat with a β-adrenergic antagonist. However, it must be noted that although cocaine is rapidly eliminated from the body through metabolism, it has several vasoactive metabolites that may be active for at least a day postexposure. In fact, although the initial coronary artery vasoconstriction resolves over a few hours, it commonly recurs due to the relative balance of metabolites even in the absence of

additional drug use. When it is safe to use β-adrenergic antagonists remains a matter of debate. However, given the limited data that early β-blockade is better than subsequent administration it seems prudent to avoid their use in the first 24 hours post-cocaine use.

Select References.

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