


Reversible Fulminant Hepatitis Secondary to Cocaine in the Setting of β -Blocker Use

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Abstract

Background. Fulminant hepatitis is acute hepatic injury with severe decline in hepatic function manifested by encephalopathy, hypercoagulable state, jaundice, renal failure, hypoglycemia, or a constellation of these symptoms in patients without preexisting liver disease. Etiologies include viral infections, hepatotoxic drugs, autoimmune diseases, vaso-occlusive diseases, sepsis, and malignant infiltration. **Case Report.** A 56-year-old man presented with acute heart failure in the setting of cocaine use. The patient subsequently developed fulminant hepatic failure manifested by acute hypoglycemia, elevated liver enzyme, and worsening liver function, which resolved over 1 week with supportive care. The patient was on β -blocker, which was stopped during the admission. He was again admitted on several different occasion for cocaine-induced acute heart failure but did not develop hepatic failure as his β -blocker was discontinued. **Discussion.** Cocaine has been known to cause hepatotoxicity in humans. However, our patient developed fulminant hepatic failure in the setting of concomitant cocaine and β -blocker use likely secondary to unopposed α -adrenergic activity and ischemic hepatopathy. The patient did not develop hepatic failure on subsequent admissions with cocaine use after discontinuation of β -blockers.

Keywords

cocaine, fulminant hepatitis, β -blocker

Background

A 56-year-old African American male veteran with combined systolic and diastolic heart failure (left ventricular ejection fraction of 25%), chronic obstructive pulmonary disease (forced expiratory volume in 1 second = 75%), HIV (on antiretroviral therapy [ART]), polysubstance abuse (tobacco, cocaine), and hypertension presented to the emergency room with sudden-onset shortness of breath and fatigue. The patient reported using cocaine (inhalational) on and off for past year and used cocaine the day of presentation. He also had history of artificial intracardiac defibrillator removal due to implant infection, thoracic aortic artery aneurysm, atrioventricular nodal reentry tachycardia s/p ablation, and left ventricular thrombus currently on rivaroxaban for anticoagulation. His last CD4 count was 490/ μ L. His home medications included losartan, bumetanide, abacavir, allopurinol, dolutegravir, emtricitabine, eplerenon, metoprolol succinate, rivaroxaban, sertraline, trimethoprim-sulfamethoxazole, albuterol, levothyroxine, and losartan. The patient reported compliance with all his medications.

On examination, the patient was found to be disheveled, malnourished, anxious, and restless. He was afebrile, mildly

tachycardic with pulse rate between 100 and 110 beats per minute, and hypertensive with blood pressure of 162/105 mm Hg. In addition, physical examination showed mild bibasilar crackles and expiratory wheeze, elevated jugular venous pressure without peripheral edema. The remainder of the physical examination was unremarkable. At this time, he was found to have positive urine toxicology screen for cocaine only. He also had hypothyroidism (thyroid stimulating hormone = 50 μ IU/mL, free T4 = 0.35 ng/dL), normo-

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cytic, normochromic anemia (hemoglobin = 12.2 g/dL), mildly elevated serum creatinine (Cr = 1.4 mg/dL), and an elevated serum brain natriuretic peptide (2279 pg/mL) that was comparable to his baseline brain natriuretic peptide. Other laboratory values including complete blood count, basic metabolic panel, levetiracetam, troponin I, prothrombin time/international normalized ratio (PT/INR), partial thromboplastin time, serum fibrinogen, and D-dimer were within the normal limits. His chest radiograph showed mild pulmonary congestion with small pleural effusions and cardiomegaly. His electrocardiogram showed sinus tachycardia, left axis deviation, low-voltage QRS, and poor R-wave suggestive of an inferior old infarct.

The patient was admitted to the ward for an acute exacerbation of chronic heart failure in the setting of cocaine use and was started on intravenous (IV) bumetanide for diuresis. All his home medications were resumed with the exception of metoprolol in light of cocaine use. He showed clinical improvement over the next day. However, on the third day of admission, the patient became confused and lethargic, and was found to be severely hypoglycemic (blood sugar = 16 mg/dL). The patient did not have diabetes mellitus and had never used insulin or any anti-hypoglycemic agents. He was transferred to the intensive care unit and was given IV dextrose that improved his hypoglycemia, but he had repeated episodes of hypoglycemia over the next couple of days requiring continuous dextrose infusion. At the same time, his renal function also started to decline with progressively worsening serum Cr levels and hyperkalemia (Cr = 1.5 mg/dL, serum potassium = 7.4 meq/mL). Concurrently, his liver enzymes started to increase and liver function also started to decline (aspartate aminotransferase [AST] = 882 U/L, alanine aminotransferase [ALT] = 1745 U/L, alkaline phosphatase = 285 U/L, total bilirubin = 2.3 mg/dL, and PT/INR = 19.9/1.7).

Given patient's HIV status, an extensive workup was done for infectious hepatitis including viral markers, fugal antigen and antibodies, and blood and urine cultures, which were negative for any infectious pathology. He was given IV vitamin K, while his ART, rivaroxaban, losartan, and trimethoprim/sulfamethoxazole were stopped in light of acute hepatic and renal failure. His liver and renal functions continued to worsen, peaking on the fifth day of admission (AST = 4285 U/L, ALT = >8000 U/L, alkaline phosphatase = 333 U/L, total bilirubin = 3.5 mg/dL, PT/INR = 95.9/12.5, and ammonia = 51 μ g/dL). An abdominal ultrasound revealed normal liver and biliary tract. A liver biopsy was contemplated but was not done in view of ongoing coagulopathy secondary to liver failure. He was managed symptomatically with oxygen, dextrose, vitamin K, diuresis, and close monitoring. His liver and renal function slowly improved over the next week and the patient showed remarkable clinical improvement. He was discharged on eighth day of admission with markedly improved laboratory values at the time of discharge (AST = 134 U/L, ALT = 531 U/L, alkaline phosphate = 244 U/L, total bilirubin = 1.4 mg/dL,

PT/INR = 16.4/1.3, and Cr = 1.1). In light of active cocaine use, his β -blocker was not resumed on discharge. His ART was restarted at the time of discharge.

Initially, the diagnosis of congestive hepatopathy and cardiorenal syndrome in the setting of congestive heart failure (CHF) was considered, but his heart failure was deemed too mild and had significantly improved by the time of manifestation of liver failure. Given such severe and hyperacute derangement of liver functions, that improved rapidly, a diagnosis of fulminant hepatitis in the setting of cocaine use was made.

The patient returned to the hospital 2 months later with similar complains. He was managed for acute CHF exacerbation in the setting of cocaine use. On this admission, however, laboratory results revealed return of liver and renal function to baseline with a normal abdominal computed tomography scan. He did not develop any hepatic or renal injury during this admission. The patient has since been admitted several times for cocaine-induced CHF exacerbation but never developed hepatic injury since discontinuation of β -blocker.

Discussion

Fulminant hepatitis is defined as acute hepatic injury with severe decline in hepatic function manifested by encephalopathy, hypercoagulable state, jaundice, renal failure, hypoglycemia, or a constellation of these symptoms in patients without preexisting liver disease. Fulminant hepatitis can be caused by viruses, hepatotoxic drugs, autoimmune diseases, vaso-occlusive diseases, sepsis, and malignant infiltration.

Our patient presented with fulminant hepatitis that manifested with all of the above-mentioned symptoms secondary to acute cocaine toxicity in the setting of β -blocker use. Cocaine has been reported to cause hepatotoxicity in humans¹⁻⁶ as well as several animal models.⁷⁻¹¹ Two previous studies found cocaine use to be associated with hepatic dysfunction manifested by elevation in liver enzymes.^{3,4} Silva et al. studied this correlation, specifically in the setting of acute cocaine use.³ Cocaine-induced periportal hepatocyte damage has been attributed to oxidative stress^{12,13} with damage to endoplasmic reticulum and mitochondria seen in the early stages of toxicity.^{11,14} However, fulminant hepatitis due to cocaine use is exceedingly rare and associated with extremely high doses of cocaine.¹⁵ Cocaine poses a theoretical risk of unopposed α -adrenergic activity in the setting of β -blocker use; however, there is conflicting evidence over the risk or even benefit of β -blocker for cocaine use.¹⁶⁻²² Our patient developed fulminant hepatitis with cocaine use while concomitantly using β -blocker and did not develop any hepatic injury on subsequent admissions. This suggests that β -blockers may have played a role in causing ischemic hepatic injury with cocaine.

We did not do histologic testing on the patient's liver given the high risk of bleeding in the early stages and rapid

improvement of clinical symptoms later on. However, the clinical picture was consistent with fulminant hepatitis. Our patient did not develop other complications of cocaine use such as hemodynamic instability, myocardial ischemia, hypoxia, intravascular thrombosis, and end-organ damage or rhabdomyolysis, which may have been responsible for the hepatic and renal injury. Given the history of heart failure, the patient may have developed hypotension prior to presentation, which may have contributed to the liver injury. However, the patient presented with elevated blood pressure at the time of presentation and did not develop hypotension during the hospital stay. Thus, the patient's fulminant hepatitis likely emanated from ischemic injury to hepatic cells from concomitant cocaine and β -blocker use.

Conclusion

Concomitant use of β -blocker and cocaine can cause fulminant hepatic failure secondary to unopposed α -activity and physicians should avoid β -blockers in patients using cocaine.

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Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series as long as patient identifiers are not disclosed.

Informed Consent

Informed consent for patient information to be published in this article was not obtained because patient identifiers were not included in this article.

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