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Cocaine-Induced Hepatonephrotoxicity: A Case Report

Guillermo P. Gubbins, MD,* Rhett M. Schiffman, MD,† Ravindra S. Alapati, MD,‡ and Surinder K. Batra, MD*

Hepatotoxicity due to cocaine has been well described in animal models. There are few reports on cocaine-induced hepatic injury in humans; however, its link to rhabdomyolysis and renal failure is better known. We report a case of reversible acute hepatonephrotoxicity associated with recreational cocaine use. The proposed mechanisms responsible for its hepatic and renal toxicity are reviewed.

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Cocaine, an alkaloid prepared from the leaves of *Erythroxylon coca*, is recognized as one of the most dangerous illicit drugs in common use today. As cocaine abuse has escalated, cocaine-related emergency room visits, hospital admissions, cardiovascular events, and deaths due to overdose have increased throughout the nation (1). Cocaine-mediated hepatotoxicity in humans has been suspected since 1967 (2). Since then, numerous studies in mice have defined several possible mechanisms of liver injury (3,4). Cases of probable cocaine-induced liver disorders in humans have been reported only recently (4,5), and cocaine-induced nephrotoxicity has been reported with increasing frequency during the last two years (6-11). We report a case of acute, reversible hepatonephrotoxicity associated with recreational cocaine use.

Case Report

A previously healthy 35-year-old woman came to the emergency room complaining of myalgias, fever, chills, diffuse abdominal pain, diarrhea, and vomiting. The symptoms had begun four days after drinking alcohol and smoking "crack" cocaine. She also related passing dark urine two days prior to admission. The patient denied intravenous drug use, had no history of hepatitis, and had one sexual partner who did not use drugs intravenously. She worked as a janitor in a nursing home, but was not aware of recent exposure to organic solvents. She did admit to drinking one-half pint of vodka or whiskey two to three times a week.

On admission the patient's blood pressure was normal but her pulse was 120 beats/min and her temperature was 37.6°C (99.7°F). Jaundice was present along with mild hepatomegaly and tenderness in the right upper quadrant. The complete blood count was normal, but the creatinine was 468 ixmol/L (5.3 mg/dL), and blood urea nitrogen 8.6 mmol/L (24 mg/dL). The prothrombin time was 20.5 seconds (control 10.5 seconds) and the partial thromboplastin time was 38 seconds (normal 22 to 36 seconds). The bilirubin was 51 μmol/L (3.0 mg/dL [2.5 mg/dL direct]), SGOT 1,711 IU/L (normal < 33 IU/L), SGPT 9,295 IU/L (normal < 40 IU/L), alkaline phosphatase 131 IU/L (normal 0 to 100 IU/L), and creatine phosphokinase 258 IU/L (normal 0 to 190 IU/L). Ethanol was not detected in the serum. Urinalysis revealed 1+ "blood," 2+ bilirubin, and 3+ albumin. Eight red blood cells, 4 to 6 renal tubular cells in clumps, 0 to 1 hyaline casts, and 3 to 4 granular casts were seen per high power field. Urinary myoglobin was not assayed, but urinary sodium was 38 mEq/L and the fractional sodium excretion was 1.6%. The urine drug screen was positive for cocaine metabolites, morphine, codeine, and amphetamines. Serologic tests for hepatitis A and B were negative.

The patient was given supportive care. The SGOT peaked at 2,482 IU/L on the second day but administration of vitamin K quickly corrected her coagulopathy. The serum creatinine peaked at 1,547 μmol/L (17.5 g/dL) on the eighth day; however, she maintained a urine output ranging from 1,600 to 2,400 mL/24 hrs. The patient did not require dialysis and was discharged after 15 days with a serum creatinine of 371 μmol/L (4.2 mg/dL) and an SGOT of 28 IU/L.

Discussion

In the mouse, cocaine is largely detoxified by plasma and liver cholinesterases to the water-soluble, nontoxic metabolites benzoyl eegonine and eegonine methyl ester which are excreted in the urine. However, a minor oxidative pathway, centered around the tropane nitrogen, is believed to be responsible for the generation of hepatotoxic metabolites (1,3,4). Two mechanisms have been proposed to account for the production of these hepatotoxic metabolites in man. The first of these involves a futile, enzymatically catalyzed cycling between N-hydroxycocaine and norcocaine nitroxide, which depletes intracellular NADPH, thereby reducing intrahepatic glutathione. As a consequence, cellular concentrations of hydrogen peroxide and superoxide radicals, which are generated by normal cellular metabolism, reach toxic levels resulting in lipid peroxidation of the cellular membranes and cell wall disruption (3). The second proposed mechanism is based on the further oxidation of norcocaine nitroxide to the extremely reactive nitrosionium ion which also depletes glutathione. Catecholamines, whose circulating

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*Division of Gastroenterology, Henry Ford Hospital.
†Bone and Mineral Division, Henry Ford Hospital.
‡Formerly Division of Gastroenterology, Henry Ford Hospital. Currently Anaheim Family Practice, Anaheim, CA.

Address correspondence to Dr. Batra, Division of Gastroenterology, Henry Ford Hospital, 2799 W Grand Blvd, Detroit, MI 48202.
levels are elevated as a consequence of cocaine use, may contribute by causing liver damage directly or by serving as cofactors for the oxidation of norcocaine nitroxide to the nitrosonium ion (4).

It has been suggested that individuals with low plasma pseudocholinesterase activity could be especially susceptible to the hepatotoxicity of cocaine because more cocaine may be shunted through the oxidative bioactivation pathway. Similarly, individuals deficient in glucose-6-phosphate dehydrogenase would have an increased risk for cocaine-induced hepatotoxicity because they generate fewer reducing equivalents (NADPH) than do normal individuals (3). Finally, cytochrome P<sub>450</sub> oxidase system inducers, such as ethanol and phenobarbital, which potentiate cocaine-induced hepatotoxicity in mice, could play a similar predisposing role in human subjects.

The only report of subclinical cocaine hepatotoxicity appeared in 1967 (2). Of the 89 heroin users evaluated at a psychiatric institution, most of whom were also users of cocaine, six were jaundiced and 80% of the patients had serum enzyme abnormalities which returned to normal after abstinence. However, the contribution of cocaine to hepatotoxicity could not be dissociated from that of heroin; and viral hepatitis, which is prevalent among intravenous drug users, was not excluded serologically. Considering the large number of people who abuse cocaine, it is surprising that cases of overt hepatotoxicity are so rare (4-6); however, the susceptibility to liver damage from cocaine is influenced by so many different factors that frank hepatotoxicity may not become a common feature of cocaine addiction (4). It is possible that ethanol, by inducing cytochrome P<sub>450</sub>, predisposed our patient to cocaine hepatotoxicity. Glucose-6-phosphate dehydrogenase and plasma pseudocholinesterase levels were not measured.

Cocaine abuse has been linked recently to rhabdomyolysis and acute renal failure (6-11). The mechanisms for this are not completely understood; however, the drug is known to cause hyperpyrexia by affecting the temperature-regulating center in the hypothalamus (1) and can also induce seizures and hyperactivity. Each of these factors may contribute to cocaine-induced rhabdomyolysis (1). The renal failure associated with cocaine abuse and rhabdomyolysis is usually nonoliguric, self-limited, and seldom requires dialysis (6). Factors other than myoglobin, however, may contribute to the development of acute renal failure in cocaine intoxication and may alter the course of the

**References**