Tubulointerstitial Injury and Drugs of Abuse

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Drug abuse is widespread in many populations, and patients abusing illicit substances are at a significantly increased risk of kidney injury. The tubulointerstitial compartment is a common target of these nephrotoxic agents. This review will cover some of the common illicit drugs and will focus on the tubulointerstitial injuries seen in the setting of drug abuse. Agents addressed in this review are synthetic cannabinoids, "bath salts," ecstasy, anabolic steroids, inhaled solvents, heroin, and cocaine. The most frequent biopsy findings are those of acute tubular necrosis and acute interstitial nephritis. Unfortunately, histology is often unable to sufficiently narrow the differential diagnosis and point to a single likely cause. A high suspicion for drug abuse as a potential cause of kidney injury is needed to identify the patients for whom this is the cause of their kidney failure. Toxicology screens are often of little use in identifying patients using emerging drugs of abuse.

Key Words: Drug abuse, Nephrotoxicity, Acute kidney injury, Acute tubular necrosis, Interstitial nephritis

INTRODUCTION

Based on a 2013 survey conducted by the National Institute on Drug Abuse, it is estimated that 9.4% of the US population aged 12 years and older has used an illicit drug within the last 30 days.[1] There is a broad spectrum of kidney injury and toxicity seen in the setting of drug abuse and this review focuses on tubulointerstitial injury caused by drugs of abuse. Unlike the wide variety of morphology that can be seen in glomerular disease, the tubulointerstitial compartment is much narrower in its histologic expression of acute injury. The two main patterns of acute tubulointerstitial injury seen in drug abuse are acute tubular necrosis (ATN) and acute interstitial nephritis (AIN) (see Fig 1). In contrast to the relatively limited histologic patterns, the list of causes for these tubulointerstitial injuries is extremely long. It is critical to keep illicit drug use in the differential diagnosis for kidney injury and to specifically inquire about and evaluate for the use of illicit drugs in the setting of AKI. Many of the newer designer drugs will not show up in standard toxicology screens, making it more difficult to detect their use. This article will cover some of the emerging and major classes of drugs of abuse and their reported tubulointerstitial pathologies (see Table 1).

SYNTHETIC CANNABINOIDS

Synthetic cannabinoids (SC) became popular drugs of abuse around 2009 and are typically smoked as a marijuana alternative. They are sold under a variety of brand names including "spice" and "K2," are often readily available at convenience stores, smoke shops, and over the Internet. These drugs are chemically distinct from delta-9-tetrahydrocannabinol, the active ingredient in marijuana, and are not detected on routine drug screens. Chemical detection currently requires chromatography and mass spectroscopy. Cases of SC toxicity often cluster geographically, which may reflect the appearance of a new SC or ingestion of a batch of SC with a high level of toxic adulterants.[2]

From 2010 to 2015, physicians in the Toxicology Investigators Consortium treated 456 patients for SC intoxication, and in 277 of these cases, SC was the sole toxicologic agent. In these 277 cases, AKI was present in 4% of patients.[3] The largest series focusing on SC nephrotoxicity was reported by the CDC and involved a multistate investigation over approximately 9 months in 2012, which identified 16 patients.[4] The CDC report details 16 young patients between the ages of 15 and 33 years who presented to the emergency department after SC use and were hospitalized with AKI. Presenting symptoms included nausea, vomiting, and abdominal, flank and/or back pain. The median peak serum creatinine in this group was 6.7 mg/dL (range 3.3-21 mg/dL) and occurred at a median of 3 days after symptom onset (range 1-6 days). Kidney biopsy was performed in 8 patients and showed ATN in 6 patients and features of AIN in 3 patients. All patients reportedly regained kidney function during hospitalization but 1 patient was discharged before creatinine normalized. Mass spectroscopy detected several different SCs and their metabolites. No single SC product explained all the cases.[4]

Smaller series and also multiple individual cases of SC nephrotoxicity have been reported. Bhanushali and colleagues[5] reported 4 cases of oliguric AKI associated with SC use from University of Alabama at Birmingham. All these patients presented with nausea and vomiting, peak median serum creatinine was 13.5 mg/dL (range 3.2-15.2 mg/dL), and all had improvement of kidney function without specific treatment or renal replacement therapy. Three of the four patients were biopsied and all biopsies showed ATN. Additional individual cases[6-8] including one highlighting a patient who developed SC-associated hyperemesis and subsequent rhabdomyolysis and AKI[9] are in the medical literature.

The mechanism of AKI in SC toxicity is likely multifactorial. Volume depletion due to nausea and vomiting appears to play a role in many of cases. Adulterants present in the SC formulations may also be responsible for direct tubular injury and could potentially be associated with an allergic response resulting in AIN. Cannabinoid receptors have been demonstrated in kidney tubular

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Financial Disclosure: No funding was used for the writing of this article and the authors have no financial or other conflict of interest to report.

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1548-5595/$36.00

http://dx.doi.org/10.1053/j.ackd.2016.09.008

cells[10] and it is possible that SCs, which are direct agonists of these receptors, cause dysregulation of the endocannabinoid system, resulting in AKI.[11]

SC abuse should be considered, especially in young and healthy patients who present with otherwise unexplained AKI. Because SC will not appear on standard toxicology screens, a history of ingestion/inhalation should be specifically sought. Cases of suspected SC poisoning should be reported to the state health department and regional poison center so that outbreaks of SC toxicity can be recognized earlier.

SYNTHETIC CATHINONES ("Bath Salts")

"Bath salts" are an emerging drug of abuse. Unlike what one dissolves in a bathtub, they are composed of beta-ketone amphetamine analogs derived from cathinone, a naturally occurring amphetamine analog found in the *Catha edulis* plant.[12] Like SCs, bath salts are not detected on routine drug screens and should be suspected in patients with negative toxicology screening who present with hallucinations, paranoia, confusion, or agitation. Reports of acute kidney injury after bath salt intoxication are predominantly attributed to ATN. Adebamiro and Perazella[13] reported recurrent episodes of AKI in a patient abusing bath salts. Although no biopsy was performed, urine microscopy showed tubular epithelial cells, and FE_{Na} was 2%, consistent with ATN. McNeely and colleagues[14] reported a case of bath salt use that presented with severe hyperthermia, hyperkalemia, rhabdomyolysis (with creatine phosphokinase > 200,000 U/L), shock, disseminated intravascular coagulation, and dialysis-dependent AKI. Based on the initial presentation, sepsis was clinically suspected, but cultures were negative and only after his family reported his illicit drug use was the association made. Additional individual cases of bath salt intoxication resulting in ATN have been also been reported.[15,16]

The tubular injury caused by bath salts is likely multifactorial. They inhibit reuptake of monoamines, including dopamine and norepinephrine, causing a surge in sympathetic activity.[12] This may result in vasoconstriction and hypoperfusion of kidneys and muscles resulting in ATN and rhabdomyolysis. There may also be direct tubular cell toxicity from the bath salts or their metabolites, but this has not been specifically studied.

3,4-METHYLENEDIOXYMETHAMPHETAMINE ALSO KNOWN AS "Ecstasy"

Ecstasy is an amphetamine derivative and common drug of abuse in college students, 39% of whom on some campuses admit to use within the last year.[17] 3,4-Methylenedioxymethamphetamine is most often taken at parties because of its reported ability to increase energy and sociability and induce euphoria. Although the clinical manifestations of ecstasy abuse are myriad, the predominant kidney manifestations are those of AKI and hyponatremia, which have been extensively reviewed by Campbell and Rosner.[18] The first case of AKI associated with ecstasy was reported in 1992, and although no biopsy was performed, AKI in this case was likely secondary to nontraumatic rhabdomyolysis.[19] Rhabdomyolysis in ecstasy use is multifactorial, relating to hyperpyrexia, increased exertion, and direct myocyte toxicity.[18]

Hyponatremia is one of the distinguishing features of ecstasy-associated AKI. The major factors in the development of hyponatremia in this population appear to be: (1) ecstasy-induced thirst; (2) counseling at the party scene to drink plenty of fluids when using; and (3) ecstasy-induced secretion of arginine vasopressin.[18] This elevation in arginine vasopressin inappropriately reduces the ability of the kidney to excrete free water rapidly enough to keep up with intake, resulting in concentrated urine despite serum hypo-osmolality.

CLINICAL SUMMARY

- Drug abuse is prevalent, and emerging drugs of abuse are typically not detected on standard toxicology screens, making it challenging to identify their nephrotoxic potential.
- Illicit drug use should be considered in the differential diagnosis of any patient presenting with AKI, even in the setting of negative toxicology screens.
- A wide variety of illicit substances display nephrotoxic effects that most commonly manifest histologically as acute tubular necrosis or acute interstitial nephritis.
- As biopsy findings of acute tubular necrosis and acute interstitial nephritis have a broad differential diagnosis, detailed clinical-pathologic correlation is needed to identify kidney injury due to drugs of abuse.

ANABOLIC ANDROGENIC STEROIDS AND NUTRITIONAL SUPPLEMENTS

Anabolic androgenic steroids (AAS) are hormones that include testosterone and its synthetic derivatives. Illicit use of AAS has been longstanding among athletes seeking a performance advantage, but research suggests that use is more widespread. AAS use often has a later age of onset than other drugs of abuse, with only 22% of users starting before age 20. An estimated 2.9-4.0 million Americans between ages 13 and 50 have used AAS, and within this group, approximately 1 million will become long-term users who exhibit AAS dependence.[20] In selected populations, such as weightlifters and bodybuilders, the prevalence of AAS abuse is much higher, with up to 44% admitting use in 1 survey.[21] The vast majority of AAS users also take an abundance of other nutritional supplements including creatine powder, amino acids, ephedrine, and high doses of vitamins. Because of this polypharmacy, it is often difficult to determine the specific agent responsible for kidney injury in these patients.

Focusing on tubulointerstitial pathology seen in AAS and supplement abusers, both AIN and ATN have been reported. Daher and colleagues[22] reported 2 cases of biopsy-proven AIN in the setting of AAS use coupled with a veterinary vitamin supplement containing high levels of vitamins A, D, and E. Both patients presented