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CLINICAL QUIZ

"Smoking" guns: Answers

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The diagnosis

Answer 1: Synthetic cannabinoid-induced acute kidney injury

Toxicology studies identified AB-FUBINACA, a fifth generation synthetic cannabinoid (SC), in the urine (450 ng/mL) and serum (52 ng/mL). Acute kidney injury (AKI) secondary to SCs was brought to international attention in a report from the U.S. Centers for Disease Control and Prevention in February 2013 [1] which detailed 16 cases of AKI after SC use in six states. A case series of four patients from Alabama, all from the same county, also implicated SCs as a cause of AKI [2]. An additional case has since been reported [3]. This is the first report of a fifth generation SC associated with AKI.

SCs, commonly referred to as "Spice," are designed to bind to the same cannabinoid receptors (designated CB1 and CB2) as the active compound in marijuana, delta-9 tetrahydrocannabinol (THC). Many SCs demonstrate a high affinity for CB1 and CB2 despite having markedly different chemical structures from THC; consequently, these compounds are also referred to as "synthetic marijuana" or cannabimimetics. SCs are designed and synthesized in clandestine laboratories. Plant material/inactive vegetable matter is soaked in solvent containing the dissolved SC or the SC is sprayed directly onto the matter [1, 4]. This material is then dried and smoked. The U.S Drug Enforcement Administration (DEA) has placed multiple SCs into Schedule I of the Controlled Substance Act (CSA), including AB-FUBINACA [5–7]. However, illicit use continues as new drugs are constantly being designed, and many of the older compounds remain commercially available under the guise of herbal incense, bath additives, or air fresheners with the label "not for human consumption." The illegal use is further encouraged by affordability, expectation of an intense high, and avoidance of detection by commonly used urine drug tests. The synthetic drug industry is a growing market. In the high school age group, 8–11 % of seniors have reported use [8].

There are countless street and commercial names for SC-containing products (Table 1)—with these names having no correlation with the presence of a particular SC. These drugs are made in laboratories with no quality or safety controls, and thus there is great variability amongst these products in terms of ingredients, potentially toxic preservatives, adulterants, and concentration of active SC [4]. There is no assurance that

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Table 1 Some synthetic cannabinoids

Commercial and street names of products	Isolated chemical products per generation/class based upon DEA placement in the Schedule 1 drug listing or new chemical materials
Albino Rhino Buds	First generation:
Arctic Spice	-JWH-018;-073;-200
Aroma	-CP-47;-497;-47,497 C8 homologue
	-Cannabicyclohexanol
Barely Legal	Second generation:
Black Box	-AM-2201
Black Mamba	-JWH-019
Bliss	-JWH-250
Bombay Blue	-RCS-8
Brain Freeze	
Bunker Buster	
Buzz	
Caneff 5 Star	Third generation:
Chill Out	-UR-144
Chill X	-XLR-11
Chillin XXX	-AKB48
Clown Loyal	
D-Raw	Fourth generation:
Dark Matter	-PB22
Dream	-BB22
Everlast	Fifth generation:
Experience	-AB-FUBINACA
	-ABPINACA
	-ADBICA
Fake Weed	
Flame 2.0	
Fusion	
Galaxy	
Genie	
Herbal Incense	
K2[a]	
K2-Blonde	
K3	
Kronic	
Lava	
Magic	
Mojo	
Mr. Happy	
Phantom Wicked Dreams	
Smoke'n'Skulls	
Spice[a]	
Spice Diamond	
Spice Gold	
Spice K2	
Spike 99	
Yucatan Fire	
Zombie 2010	

DEA, Drug Enforcement Agency.

[a] Spice and K2 is often used to collectively refer to synthetic cannabinoid products.

"Brain Freeze" always contains AB-FUBINACA or that "Lava" always contains XLR-11. The variation in product content and the increasing use has resulted in several "outbreaks" of adverse health effects which occur in distinct regional and temporal cohorts [1, 2].

Answer 2: The mechanism of SC-induced AKI remains speculative

Two findings provide the theoretical basis for a direct nephrotoxic effect: (1) animal studies have shown that after inhaled SC exposure these compounds can be isolated directly from the kidney [9]; (2) both cannabinoid receptors are expressed in kidney tissue. Most SCs are full agonists of these receptors (as compared to THC which is only a partial agonist), but increasing activation of a naturally occurring receptor, even by a non-endogenous compound, seems unlikely to be causative of AKI. Some researchers have claimed that the presence of fluorine or other side-chains in some SC may be responsible for the injury to the kidney, similar to the injury which results from fluorinated anesthetics, such as methoxyflurane [10]. Others implicate contamination with heavy metals or other unsuspected toxic substances. In this case, the AKI is likely to be secondary to hypovolemia induced by nausea and vomiting, resulting in kidney ischemia. Kidney biopsy, although not performed in our case, has shown evidence of tubular injury (acute tubular necrosis) and/or interstitial nephritis [1–3].

Answer 3: The only laboratory study not consistent with the diagnosis was the positive urine drug screen for THC

Alluded to earlier in Answer 1, SCs are often used as an alternative to marijuana because SCs are not detected by commonly used urine drug tests. Ironically in our case, the preliminary urine drug screen used an immunoassay for THC and was initially positive, though more specific toxicology studies using mass spectroscopy ultimately did not confirm THC exposure.

As a general overview, the clinical presentation of SC-induced AKI is most often nausea and vomiting (>95 % of the time). The majority of patients also have abdominal, flank, or back pain (>65 %). In almost all cases the serum creatinine level follows a relatively consistent pattern, with peak creatinine occurring within 6 days of symptom onset and improvement beginning within 3 days of the creatinine peak [1]. This pattern is consistent with the presentation of our patient. Anuric AKI is rare (<5 %). Temporary dialysis has been prescribed in 22 % of reported cases, but no patient to date has developed end-stage renal disease. Results from urinalysis are variable, but most patients have hematuria and leukocyturia, as well as some degree of proteinuria. Renal ultrasound often shows the non-specific finding of increased cortical echogenicity (75 % of the time). Rhabdomyolysis/elevated creatine kinase (CK) and hyperuricemia have been reported after SC use [2, 3, 11].

Answer 4: It is unclear whether the conducted electrical weapon encounter contributed to the elevated CK and hyperuricemia

Conducted electrical weapons (CEWs) incapacitate a subject by inducing tetany through electric stimulation [12, 13]. Therefore, muscle breakdown and AKI from rhabdomyolysis are theoretical risks. CEWs have been used by law enforcement since the 1970s. The Thomas A Swift Electric Rifle (TASER), the most common electronic weapon used by law enforcement in the USA, was devised as a non-lethal alternative to the use of a hand gun which has a 50 % mortality, for temporarily incapacitating an aggressive subject [14]. The device causes involuntary muscle contraction by stimulating peripheral motor neurons at a sub-tetanic rate [12, 13, 15].

Case reports have implied that TASER guns may cause rhabdomyolysis and AKI [16, 17]. All case reports of TASER device-associated rhabdomyolysis have occurred in the context of significant physical exertion and/or drug use (cocaine, phencyclidine). There is a lack of consensus on how much to attribute rhabdomyolysis in such an encounter to electrical weaponry. In fact, various medical experts [18] and authors of studies of conducted electrical weaponry use on healthy individuals [19–24] have argued against an association of severe rhabdomyolysis and TASER encounter. However, these medical experts are employees and company stockholders of TASER International, Inc., and most of these studies were partially funded the company.

In reviewing the studies in healthy volunteers, analysis and interpretation of the data may be misleading. For instance, the authors of a pooled analysis of five human studies (n=156) [19] reported a median change in CK of only 32 U/L when two electrodes were activated (as in our case) and a median change in CK of 303 U/L when exposure was for 10 s. However, the actual range in CK change was up to 1,821 U/L for two points of contact and up to 25,452 U/L for 10 s of exposure. The authors explain the elevation in CK by commenting on non-adherence to study protocol due to concurrent exercise training by some of the subjects (all were requested not to engage in strenuous activity for 48 h before and until the last blood draw at 24 h). Ultimately, two of the patients (1.3 %) in the pooled data had CK levels of >5,000 U/L at 24 h. Although not conclusive, as the results are confounded by exercise, these values do support that a TASER encounter could cause severe rhabdomyolysis. A more accurate analysis of risk may be when the TASER is used in the field against criminal suspects. Bozeman et al. reported only one case (<0.1 %) of rhabdomyolysis (CK 61,116 U/L 2 days after arrest) in 1,201 encounters, but again confounding the association, the suspect admitted to crack cocaine use, fled on foot, and vigorously resisted arrest [25]. In another study of 218 arrests, the use of TASER resulted in a 1 % occurrence of "mild rhabdomyolysis and myoglobinuria" [14].

Conclusions

This clinical quiz highlights for the nephrology community an emerging cause of acquired AKI, namely, synthetic drug use. SCs are available in all communities, and their use is increasing, especially among adolescents and young adults. The American Association of Poison Control Centers reports "exposure calls" numbering in the thousands since 2011 [26]. The isolation of AB-FUBINACA in our patient highlights an ever evolving threat as new SCs are developed in an effort to circumvent regulatory efforts. Finally, although using a CEW to subdue an agitated or dangerous suspect has not conclusively been associated with rhabdomyolysis, by its mechanism of incapacitation (involuntary muscle contraction), it should be considered as a potential cause of rhabdomyolysis.

Conflict of interest None.

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