

## Clinical Report

# Synthetic marijuana and acute kidney injury: an unforeseen association

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### Abstract

Synthetic cannabinoids (SCs) have emerged as drugs of abuse with increasing popularity among young adults. The potential renal complication related to the abuse of SC was not recognized until recently. Here, we present a case of severe acute kidney injury (AKI) that developed after inhalation of SC in an otherwise healthy young patient. A kidney biopsy revealed severe acute tubular necrosis, and supportive management resulted in the recovery of the kidney function. Herein, we briefly summarize the only two previous reports (a total of 21 cases) on the association between SC abuse and renal dysfunction and identify the common aspects in all observations.

**Keywords:** acute kidney injury; cannabinoids; cannabis; synthetic marijuana

### Introduction

Synthetic cannabinoids (SCs) are a large group of chemicals that were originally developed for research on the pharmacology of cannabinoid receptors [1]. They can produce subjective effects similar to those of cannabis (i.e. delta-9-tetrahydrocannabinol or THC) and have recently emerged as drugs of abuse with steadily increasing popularity among adolescents and young adults [2]. While a number of adverse health effects related to the abuse of SC have previously been reported, the potential renal complication was not recognized until recently [3, 4]. Here, we present a case of acute kidney injury (AKI) associated with SC use and briefly summarize pertinent available data.

### Case

A 22-year-old man without prior medical problems presented to the Emergency Department at the University of Florida with nausea, vomiting and flank pain for 3 days. His blood pressure was 123/68 mmHg with a pulse of 62, and the remainder of his physical examination was unremarkable. Laboratory studies revealed AKI with a serum creatinine level of 623  $\mu\text{mol/L}$  (7.05 mg/dL), blood urea nitrogen of 12.5 mmol/L (35 mg/dL) and an active urine microscopy. [Table 1](#) summarizes the pertinent laboratory findings. The patient denied the use of any obvious nephrotoxic medication, except for two tablets of ibuprofen (unknown dose) for flank pain. Upon further questioning, he admitted to smoking 'fake weed' occasionally; the last time being 3 days prior to admission, after which his

symptoms started and he felt increasingly sick. Urine drug screen (including amphetamine, benzodiazepine, barbiturate, cannabinoid, cocaine and propoxyphene) was performed on admission and was negative. A renal ultrasound demonstrated bilateral echogenic kidneys without evidence of hydronephrosis, stones or masses. His renal function continued to deteriorate despite aggressive volume repletion over the next 2 days. A renal biopsy was performed which showed acute tubular necrosis with focal tubular atrophy and flattened epithelium, loss of brush border, casts, vacuolization and mitosis. Vessels were unremarkable, with no significant staining on the immunofluorescence and no deposits on electron microscopy. With supportive management, the patient's renal function started to recover and he did not require any renal replacement therapy. He was discharged home a few days later with a serum creatinine level of 221  $\mu\text{mol/L}$  (2.5 mg/dL).

### Discussion

Two endogenous cannabinoid receptors have so far been identified: CB1 and CB2 [1]. CB1 receptors are predominantly found in the central and peripheral nerve terminals, where they portend an inhibitory effect on  $\gamma$ -aminobutyric acid (GABA). CB1 activation is responsible for the neuropsychiatric effects of SC such as elation, irritability and anxiety. CB2 receptors are located in tissues related to the immune system (e.g. spleen) and are suggested to have a role in the control of emesis and pain. These two receptors are also expressed within human glomeruli predominantly by podocytes [5]. Animal studies suggest that activation of these receptors could have a protective effect on diabetic nephropathy through reduction in albuminuria [5, 6], and CB1 might have

**Table 1.** Pertinent laboratory findings

Source	Parameters	Patient's values	Reference range	
Serum	Sodium (mEq/L) [mmol/L]	133 (133)	136–145 (136–145)	
	Potassium (mEq/L) [mmol/L]	3.4 (3.4)	3.3–5.1 (3.3–5.1)	
	CO <sub>2</sub> (mEq/L) [mmol/L]	23 (23)	22–30 (22–30)	
	BUN (mmol/L) [mg/dL]	12.5 (35)	2.1–7.1 (6–20)	
	Creatinine (μmol/L) [mg/dL]	623 (7.05)	71–106 (0.8–1.2)	
	Calcium (mmol/L) [mg/dL]	2.15 (8.6)	2–2.65 (8–10.6)	
	Phosphate (mmol/L) [mg/dL]	1.55 (4.8)	0.9–1.45 (2.7–4.5)	
	Uric acid (μmol/L) [mg/dL]	625 (10.5)	0.0–416 (0.0–7.0)	
	AST (U/L)	26	0–37	
	ALT (U/L)	13	0–41	
	CK (U/L)	338	30–170	
	Urine	Sodium (mEq/L) [mmol/L]	38 (38)	–
		Creatinine (μmol/l) [mg/dL]	6364 (72)	–
		Protein (g/L)	2.7	–
Myoglobin		Negative	Negative	
Eosinophils		Negative	Negative	
Microscopy		WBC+, RBC+, protein+, Hb+, ketones+	Negative	

a role in protecting kidneys from injury and fibrosis through improvement in insulin resistance in diabetes [7].

SCs are non-polar agonists of CB1 and CB2 receptors with variable affinity/selectivity for each one [1]. Compared with THC, SCs have a substantially higher potency often resulting in exaggerated neuropsychiatric effects. Little is known about pharmacology of SC. It has been suggested that detoxification and elimination of these products initially take place through hepatic cytochrome P450 oxidation followed by conjugation and renal excretion [1].

The recreational use of SC has been increasing since they were marketed a few years ago in part due to their easy accessibility and relatively low cost. They are distributed under names such as 'Spice' and 'K2' within packages that frequently bear labels such as 'incense' or 'aromatherapy'. Due to their structural dissimilarity to cannabis, these products (also referred to as 'synthetic marijuana' and 'fake weed') were legal when they first became popular. However, mounting evidence on their harmful effects led to state and federal legislations [8]. Recently, the US Drug Enforcement Administration temporarily designated five of these chemicals as Schedule-I substances. SCs are structurally unrelated to THC and therefore, routine drug screening tests do not detect them. However, specific techniques with limited availability have recently made it possible to measure SC and their metabolites in the urine.

While a variety of adverse physical and neuropsychiatric effects associated with SC abuse have previously been recognized [8, 9], emerging reports are suggestive of potential nephrotoxicity of these products. For the first time in the medical literature, in 2012 Bhanushali *et al.* reported four cases of AKI associated with SC abuse in Alabama [3]. All patients presented with nausea, vomiting and abdominal pain after using SC; three had severe oliguric AKI for which a renal biopsy was performed and demonstrated acute tubular necrosis (ATN). Patients recovered with supportive management and none required renal replacement therapy. In February 2013, Centers for Disease Control and Prevention (CDC) published a notification in which AKI was identified as an unanticipated complication of the SC abuse [4]. Based on this report, 16 patients from five different states in the USA had been hospitalized due to SC-associated AKI in 2012. The median age of the patients was 18.5 years and all but one had nausea and vomiting. Half of the patients underwent

a renal biopsy; ATN was the most common histologic finding (six patients), while acute interstitial nephritis was seen in three of the eight patients. Corticosteroids were used in four patients, and five patients required dialysis. No mortality was reported.

The pathogenesis of SC-associated AKI remains to be clarified. Rhabdomyolysis seems to be an unlikely possibility. In our case, creatine kinase (CK) was only mildly elevated, urine myoglobin was negative, and there were no signs of pigment deposition in the renal biopsy. ATN due to prolonged pre-renal azotemia secondary to nausea and vomiting is another possibility. However, in this case, the patient had normal pulse and blood pressure on presentation, had experienced nausea but very limited vomiting, and had not noticed any change in urine volume prior to admission. Given the fact that all reported cases are young and without previous illness or history of taking medications, development of such severe AKI simply due to low fluid intake and intravascular volume depletion, although possible, seems to be less likely as the main cause of AKI in these patients. We propose that toxic, rather than ischemic, tubular injury due to direct effect of SC (or potentially other added constituents such as heavy metals) could be responsible.

The similarities among the 21 thus far reported cases of SC-associated AKI from various geographic areas are illustrative of a certain pattern: first, 95% of the reported cases (20 out of 21) are male, with nausea, vomiting and abdominal pain being the most common presentation (Table 2). In an anonymous online survey by Winstock and Barratt, 79.6% of 953 recent users (as defined by SC use within the previous 12 months) were male [9]. Second, tubular injury is the predominant histologic finding in cases where a renal biopsy has been performed (10 out of 12). Third, although most patients recover with supportive management, nearly 25% have so far required renal replacement therapy (5 out of 21).

Our case supports previous reports of SC-associated AKI and suggests that nephrotoxicity could be a complication of these products. One limitation of our observation as well as previous similar cases is that these reports are only suggestive but not conclusive evidence of a causal relationship. They are meant to increase the awareness of practicing physicians of the possibility of a previously unrecognized association. In fact, similar to other illicit drugs, the exact ingredients of the SC packages are likely

**Table 2.** Demographic and clinical characteristics of the reported patients

Reference	Case	Age	Gender	Presenting symptoms	Urine microscopy	Peak creatinine ( $\mu\text{mol/L}$ ) [mg/dL]	Additional information
Bhanushali <i>et al.</i> [3]	1	20	M	Nausea, vomiting	Proteinuria, WBCs, occasional muddy brown casts	1211 (13.7)	Biopsy revealed acute tubular necrosis and nonspecific calcium oxalate crystals, did not need RRT Biopsy revealed mild acute tubular injury and non-specific calcium oxalate crystals, did not need RRT Biopsy revealed acute tubular injury, did not need RRT
	2	23	M	Nausea, vomiting	Proteinuria, RBCs	1343 (15.2)	
	3	26	M	Nausea, vomiting, abdominal pain, diarrhea	Proteinuria, WBCs, RBCs, 3+ leukocyte esterase	1175 (13.3)	
	4	30	M	Nausea, vomiting, abdominal pain, diarrhea	Normal	283 (3.2)	
Centers for Disease Control and Prevention [4]	5	19	M	Nausea, vomiting, abdominal pain	WBC's, RBC's, RBC/ granular casts	460 (5.2)	None of the patients reported pre-existing renal dysfunction, biopsy was done in eight cases: 6 of 16 had acute tubular injury and 3 of 16 showed acute interstitial nephritis, 4 patients received corticosteroids and 5 required dialysis, there was no mortality
	6	15	M	Nausea, vomiting, abdominal pain	WBCs, RBCs, RBC/ granular casts, eosinophils	601 (6.8)	
	7	21	M	Nausea, vomiting, flank pain	WBCs, RBCs, granular casts, epithelial casts	557 (6.3)	
	8	18	M	Nausea, vomiting, abdominal pain	WBC's, hyaline casts	362 (4.1)	
	9	25	M	Nausea, vomiting, anuria	Proteinuria, RBCs, eosinophils	1856 (21)	
	10	30	M	Nausea, vomiting	WBCs, RBCs, RBC/ hyaline casts	796 (9.0)	
	11	18	M	Nausea, vomiting, abdominal pain	Proteinuria, WBCs	583 (6.6)	
	12	33	M	Nausea, vomiting	Not available	292 (3.3)	
	13	27	M	Flank pain	Proteinuria, small blood	415 (4.7)	
	14	15	M	Nausea, vomiting, abdominal pain, back pain	Trace proteinuria	804 (9.1)	
	15	26	M	Nausea, vomiting, abdominal pain, back pain	Normal	681 (7.7)	
	16	17	M	Nausea, vomiting, flank pain	Proteinuria, WBCs, RBCs, eosinophils	937 (10.6)	
	17	18	M	Nausea, vomiting, abdominal pain	Proteinuria, Blood 3+, no RBCs	849 (9.6)	
	18	18	M	Nausea, vomiting, abdominal pain	Proteinuria	486 (5.5)	
	19	15	M	Nausea, vomiting, abdominal pain	WBC's, RBCs	1017 (11.5)	
	Present case	20	15	F	Nausea, vomiting	Proteinuria, WBCs	
21		22	M	Nausea, vomiting	Proteinuria, WBCs, RBCs, trace ketones, trace hemoglobin	822 (9.3)	

to be variable with regard to the quantity of each constituent as well as the presence of other possibly added compounds and stimulants.

Based on this case, coupled with previous reports, we suggest that AKI could be a complication of SC abuse, and that health care providers caring for otherwise healthy young adults who present with unexplained AKI should inquire about SC abuse.

*Conflict of interest statement.* None declared.

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