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JSM Clinical Case Reports

Case Report

Synthetic Cannabinoids Might Lead to Kidney Injury through Elevation in Serum Myoglobin

Omar H. Maarouf* and Jerry McCauley

Renal Division, Thomas Jefferson University Hospital, USA

***Corresponding author**

Omar H. Maarouf, Renal Division, Thomas Jefferson University Hospital, 833 Chestnut St., Philadelphia PA 19107, USA, Tel: 215-503-3000, Fax: 215-503-4099, Email: omar.maarouf@jefferson.edu

Submitted: 03 July, 2021

Accepted: 06 August, 2021

Published: 08 August, 2021

ISSN: 2373-9819

OPEN ACCESS

Abstract

Synthetic cannabinoids (SC) are becoming quite popular among the younger population given its high potency and lack of detection in urine drug screens. These drugs can cause acute kidney injury severe enough to warrant renal replacement therapy. Serum myoglobin seems to be a good predictor of the severity of kidney injury after abusing SC. Our case report highlights a vital diagnostic criterion that is often missed in checking serum myoglobin in the setting of SC abuse to predict the severity of AKI that can accompany intoxication with this drug.

INTRODUCTION

Synthetic cannabinoids (SC) are laboratory-synthesized drugs of abuse designed to stimulate the endogenous cannabinoid system and are commonly referred to as "spice" or "K2" [1,2]. These products are increasingly popular given their greater potency. They are as much as 100 times more potent, when compared to the natural cannabinoid Δ9-tetrahydrocannabinol (THC). In addition, they are not detected in traditional urine drug screens [1,2]. SC are available in many forms: as cigarettes or as a liquid to be vaporized [1]. The impact of SC on health is not fully understood and SC has been associated with injury to various organ systems. Early on it was recognized that these drugs have been associated with various physical and neuropsychiatric effects, including impairment in neural brain mechanisms and psychosis [3-5]. SC have also been linked to development of arrhythmias [6,7] as well as coagulopathy, intracranial hemorrhage and immune thrombocytopenia [8]. Interestingly, in the case series by Kelkar et al., abdominal imaging performed to evaluate for intra-abdominal hemorrhage identified radiographic abnormalities most commonly in the renal system, such as perinephric stranding, hyperemia, diffuse thickening, and dilatation of the urothelial collecting system [8].

CASE PRESENTATION

We report on three cases of SC leading to various degrees of acute kidney injury (AKI) at our institution. The first is a 35-year-old man with no significant past medical history who presented to Thomas Jefferson University Hospital after having a seizure. Upon presentation to the ED, he had a rapid decline in his mental status requiring intubation and mechanical ventilation. He was tachycardic (HR 103 bpm) and slightly hypertensive on presentation (BP 163/86). His physical examination was only remarkable for red conjunctiva. A serum chemistry panel revealed the following results: sodium, 140 mEq/L; potassium, 4.2 mEq/L; bicarbonate, 21 mEq/L; urea nitrogen, 11 mg/dl; creatinine, 1.2 mg/dl; and albumin, 4.6 mg/dl. His AST & ALT on admission were within normal range. The creatinine increased to 2.9 mg/dL on the next day and his urine toxicology screen was negative. Urinalysis showed specific gravity of 1.015, 1+ protein, no glucose, blood 2+ and 6–10 red blood cells per high-power field. The spot urine protein/creatinine ratio was 0.35 g/g. Antinuclear antibody (ANA), antinuclear cytoplastic antibody (ANCA), anti-glomerular basement membrane (GBM) antibody, hepatitis screens, and HIV antibody screen were negative. Other admission laboratory studies are summarized in Table 1. The renal ultrasound demonstrated normal size kidneys (11.1 cm on right and 10.8 cm on left) with normal echogencity and no evidence of hydronephrosis. He continued to be hemodynamically stable without evidence of an infection. His girlfriend reported that they were using "SPICE" over the last 2 nights. His creatinine increased over the course of 24 hours and continued to rise, and his urine output declined. On day 5 of the admission, his creatinine peaked at 11.7 mg/dL despite intravenous fluids and without administration of any evident nephrotoxins. His creatinine kinase (CK) peaked at 2976 IU/L, which is about 10 times higher than the upper limit of normal at our lab [9] and his serum myoglobin peaked at 1903 IU/L, almost 20 times the upper limit of normal. Renal replacement therapy (RRT) was initiated. His renal function started to recover 10 days later with improving urine output so RRT was discontinued on Day 15. He was discharged home with a serum creatinine of 7.5 mg/dl which has continued to improve down to 3.6 mg/dL on his 10-day follow up post-hospitalization and down to 2.2 mg/dL on his one-month follow up post-hospitalization. The second patient is a 38-year-old woman with known diabetes mellitus type II and

Table 1: Admission laboratory results are summarized.

	Case 1	Case 2	Case 3
Age (yr)	35	22	38
Gender	Male	Male	Female
Clinical features	change MS; red eyes	status; no red eyes	lethargic; no red eyes
Admission creatinine	1.4	0.8	0.9
Peak creatinine	11.7	1.5	2.2
potassium at Cr. peak	3.3	4.3	4.1
bicarbonate at Cr. peak	21	20	22
Discharge creatinine	7.5	0.9	0.7
Renal biopsy	none	none	none
Proteinuria	0.346	none	0.08
Urine drug screen	Negative	Negative	Negative
White blood cell count (10^3/mm3)	22.3	20.4	22.4
Hemoglobin (g/dl)	8.2-13.1	11.9-14.3	6.1-11.2
platelets	219-824	185-219	219-330
Serum calcium (mg/dl)	8.7-9.9	8.5-9.1	8.7-9.6
Serum phosphorus (mg/dl)	5-6.8	3.1-4.1	2-5.6
Creatine phosphokinase (U/L)	2131-2976	1426-7001	49-196
Myoglobin	821-1903	297-1600	59-197
INR	0.99-1.36	1.04-1.09	1.04-1.25
Albumin	3-4.4 g/dL	3.3-4.0 g/dL	2.2-2.6
tBili	0.4-3.2 mg/dL	0.5-0.6 mg/dL	0.2-0.3
Alk-phosphatase	67-122 IU/L	69-94 IU/L	55-98
AST	30-95 IU/L	43-149 IU/L	19-35
ALT	30-95 IU/L	54-195 IU/L	19-29
urine RBC	6--10	3	1
urine myoglobin	negative	positive	positive
Urine blood	3+	2+	1+

depression who presented to our ED with lethargy of a few days duration. She was found to have pneumonia and admitted to the inpatient ward. On admission, her blood pressure was 130/92 with heart rate of 86 beats per minute. Her physical exam was unremarkable except for coarse crackles at the left lower base. Her creatinine on admission was 0.9 mg/dL (baseline 0.6 mg/dL) and peaked at 2.2 mg/dL on hospital day 5 with a decline in urine output; however, she had a complete recovery of her kidney function to a creatinine of 0.7 mg/dL by Day 10 without the need for RRT. Her CK level was only mildly elevated to 196 IU/L however her myoglobin was significantly elevated at 197 ng/ml. Her liver function tests remained normal. The UA was positive for blood (1+) with RBCs 1 per HPF and her urine myoglobin was also positive. Urine toxicology screen was negative. Other admission laboratory studies are summarized in Table 1. She has been using "K2" occasionally for over a year but had been using it more frequently in the last week leading up to admission. She has not returned for follow up in the outpatient clinic. The third patient is a 22-year-old man without any significant medical history who presented to our ED after having a tonic-clinic seizure at home for the first time. On presentation, his BP was 130/66 and he was not tachycardic (HR 74 beats per minute). His physical examination was essentially unremarkable. The serum chemistry panel revealed the following results: sodium, 138 mEq/L; potassium, 4.8 mEq/L; bicarbonate, 24 mEq/L; urea nitrogen, 5 mg/dL; creatinine was 0.8 mg/dL; glucose 177 mg/dL; and albumin, 4.0 mg/dL. Other admission laboratory results are summarized in Table 1. Urinalysis showed specific gravity of 1.009, no protein, 1+ glucose, 2+ blood with 1-3 red blood cells per high-power field. Urine myoglobin was positive. Urine toxicology screen was negative. Antinuclear antibody (ANA), antinuclear cytoplasmic antibody (ANCA), anti-glomerular basement membrane (GBM) antibody, hepatitis screens, and HIV antibody screen were negative. The renal ultrasound was unremarkable. His creatinine peaked at 1.5 mg/dL on hospital day 2, recovering back to baseline in less than a week. His CK levels peaked at 7001 IU/L and decreased to 1426 IU/L by day 3 and similarly his serum myoglobin peaked to 1600 ng/ml and decreased to 297 ng/ml. He reported using "K2" for more than a year and thinks he consumed more than his average the night he had the seizure.

DISCUSSION

To our knowledge, this is the first case series of SC-

associated AKI with documented presence of myoglobinemia as the likely culprit of acute kidney injury (AKI). The first cases of AKI associated with SC were reported in 2013 with 4 cases of severe AKI, none requiring RRT. Kidney biopsies uniformly demonstrated acute tubular necrosis (ATN) as the cause of AKI. In 2013, the Centers for Disease Control published a warning that SC can result in AKI, citing ATN followed by acute interstitial nephritis (AIN) as the most common etiologies for AKI [10]. The pathogenesis of SC-associated AKI remains unknown; however, one of the common hypotheses suspects that rhabdomyolysis is responsible for leading to severe AKI although in most cases the CK elevation did not meet threshold for the diagnostic criteria for rhabdomyolysis [11,12]. There is a single case report of a patient who developed rhabdomyolysis leading to severe AKI and requiring RRT in the setting of SC use while having been maintained on neuroleptics which have also been linked to rhabdomyolysis [13]. A more recent report describes a case of thrombocytopenic microangiopathy (TMA) in the kidney associated with SC use [14]. In another recent report, delirium secondary to SC withdrawal was associated with elevated CK and myoglobin but there was no mention of the kidney function [15].

In all three cases we report, CK levels were modestly elevated; however, there was significant elevation in serum myoglobin. Liver injury has been associated with significant elevation in serum myoglobin [16,17]. The three cases we described show no clear signs of liver injury except the elevation in serum myoglobin. In the first case who presented with the most severe AKI requiring RRT, urine myoglobin was negative which a reflection of severity of the AKI is likely. The other 2 cases had significant myoglobinemia as well as myoglobinuria. Myoglobinuria causes cast formation which can lead to intratubular obstruction and proximal tubular cell injury [18,19]. SC might cause myoglobin leak from the liver despite lack of significant liver injury. The modest elevation in CK argues against a significant muscle injury. The findings in this case series warrant further investigation into the pathogenesis of SC in kidney injury to better tailor therapy.

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Cite this article

Maarouf OH, McCauley J (2021) Synthetic Cannabinoids Might Lead to Kidney Injury through Elevation in Serum Myoglobin. JSM Clin Case Rep 9(2): 1188.