Acute kidney injury associated with smoking synthetic cannabinoid

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Context and objectives. Synthetic cannabinoids are illegal drugs of abuse known to cause adverse neurologic and sympathomimetic effects. They are an emerging health risk: 11% of high school seniors reported smoking them during the previous 12 months. We describe the epidemiology of a toxicologic syndrome of acute kidney injury associated with synthetic cannabinoids, review the toxicologic and public health investigation of the cluster, and describe clinical implications of the cluster investigation. Materials and methods. Case series of nine patients affected by the toxicologic syndrome in Oregon and southwestern Washington during May–October 2012. Cases were defined as acute kidney injury (creatinine > 1.3 mg/dL) among persons aged 13–40 years without known renal disease who reported smoking synthetic cannabinoids. Toxicology laboratories used liquid chromatography and time-of-flight mass spectrometry to test clinical and product specimens for synthetic cannabinoids, their metabolites, and known nephrotoxins. Public health alerts informed clinicians, law enforcement, and the community about the cluster and the need to be alert for toxicidromes associated with emerging drugs of abuse. Results. Patients were males aged 15–27 years (median, 18 years), with intense nausea and flank or abdominal pain, and included two sets of siblings. Peak creatinine levels were 2.6–17.7 mg/dL (median, 6.6 mg/dL). All patients were hospitalized; one required dialysis; none died. No alternate causes of acute kidney injury or nephrotoxins were identified. Patients reported easily purchasing synthetic cannabinoids at convenience, tobacco, and adult bookstores. One clinical and 2 product samples contained evidence of a novel synthetic cannabinoid, XLR-11 ([1-(5-fluoropentyl)-1H-indol-3-yl][2,2,3,3-tetramethylcyclopropyl]methanone). Discussion and conclusion. Whether caused by direct toxicity, genetic predisposition, or an as-yet unidentified nephrotoxin, this association between synthetic cannabinoid exposure and acute kidney injury reinforces the need for vigilance to detect new toxicologic syndromes associated with emerging drugs of abuse. Liquid chromatography and time-of-flight mass spectrometry are useful tools in determining the active ingredients in these evolving products and evaluating them for toxic contaminants.

Keywords Epidemiology; Electronspray ionization; Mass; Public health; Substance-related disorders; Spectrometry

Abbreviations: AKI, acute kidney injury; BP, blood pressure; BUN, blood urea nitrogen; Cr, creatinine; CDC, Centers for Disease Prevention; LC-TOF/MS, liquid chromatography time-of-flight mass spectrometry; SC, synthetic cannabinoid

Introduction

Synthetic cannabinoids are chemically synthesized cannabinoid type 1 (CB1) and cannabinoid type 2 (CB2) receptor agonists initially developed by research laboratories attempting to isolate and enhance desired CB2 receptor analgesic and anti-emetic effects while lessening CB1 receptor psychoactive effects.1,2 More recently, illicit laboratories have developed and marketed synthetic cannabinoids with enhanced psychoactive effects for recreational use.3 These drugs were first distributed in the United States during 2009.4 Typically, synthetic cannabinoids are manufactured in unregulated laboratories, then purchased by local distributors who dilute the drug in a solvent, spray it on dried plant materials, add chemical flavorings, and sell it to consumers, who smoke it.5 Synthetic cannabinoid product, solvent, or plant material could each contain toxic compounds.
Certain synthetic cannabinoids are more potent than delta-9-tetrahydrocannabinol (the primary active phytocannabinoid contained in marijuana). These compounds have been associated with numerous adverse effects, including emesis, tachycardia, hypertension, agitation, hallucinations, and seizures. Such effects resulted in more than 11,000 US emergency department visits during 2010 and more than 12,000 calls to poison control centers during 2011–2012. Street names include Spice, K2, herbal incense, and potpourri. Although all synthetic cannabinoids have been illegal in Oregon since April 2011, they continue to be sold over-the-counter.

In August 2012, a clinician reported to the Oregon Public Health Division a case of acute kidney injury (AKI) in a previously healthy male aged 17 years (Patient A), who admitted smoking a synthetic cannabinoid prior to onset of symptoms of nausea, vomiting, and flank pain. In response, we launched an investigation to determine the scope of the problem. Review of Oregon Poison Center data revealed an additional case (Patient B) with a similar exposure and presentation one month earlier. Ultimately, we identified nine persons who presented to Oregon and southwest Washington hospitals during May–October 2012 with AKI after smoking synthetic cannabinoid products. In this report, we present in detail the first two cases recognized, followed by the epidemiologic summary of all nine cases, the methods used to identify a causative toxin, and the efforts to mitigate ongoing risk to the public.

Methods

Case definition

Cases were defined as persons aged 13–40 years without known preexisting renal disease who had new-onset serum creatinine greater than 1.3 mg/dL (reference laboratory normal, ≤1.3 mg/dL), treated in Oregon hospitals since February 2012, and who reported synthetic cannabinoid use during the previous 2 weeks. Age range was chosen on the basis of initial case reports, expected age of synthetic cannabinoid users, and to exclude older persons with increased risk of AKI from other causes (i.e., those aged > 40 years). Onset time was chosen based on the earliest known cases of synthetic cannabinoid-associated AKI (unpublished Epi-X data, 2012). This investigation underwent Centers for Disease Control and Prevention (CDC) human subjects review. It was considered public health practice and designated institutional review board-exempt.

Case ascertainment

The Oregon Poison Center and Oregon Public Health Division conducted passive surveillance and active case-finding. We reviewed Oregon Poison Center calls submitted to the National Poison Data System that reported synthetic cannabinoid exposure; matches were reviewed for AKI per the case definition. To identify any additional cases and to promote awareness of a possible new toxicologic syndrome associated with synthetic cannabinoid exposure, we queried all directors of regional poison control centers in the US about other cases, distributed notices through Oregon’s Health Alert Network and Epi-X (italicize), sent letter to all licensed Oregon nephrologists, and issued press releases.

Case summary

We abstracted medical records to document demographic characteristics, event onset, previous medical history, medications, interventions, laboratory results, diagnosis, alternative causes, and follow-up.

Patient interviews

We conducted face-to-face or telephone interviews with patients using a standardized questionnaire regarding clinical signs and symptoms, drug use habits, synthetic cannabinoid brand and frequency of use, as well as any perceived previous adverse effects. We also collected information about ease of access, purchase venues, and perceptions about legality and health risk related to synthetic cannabinoid use.

Clinical and product specimen testing

Clinical specimens (e.g., urine, serum, and biopsy tissue) were collected and frozen as soon as possible after symptom onset. Renal biopsy specimens were processed for light microscopy, immunofluorescence, and electron microscopy. Samples collected from original products smoked by patients were tested using the same method as clinical specimens.

Toxicologists tested specimens using previously described methods. Compounds from a synthetic cannabinoid product extract were separated by polarity using liquid chromatography, and individual retention times were noted. Next, the eluant was processed through time-of-flight mass spectrometry (LC-TOF/MS; Agilent LC 1200 TOF/MS 6230; Agilent Technologies, Inc., Santa Clara, California, USA). LC-TOF/MS allows estimation of molecular mass with 1000 times more accuracy (i.e., exact mass) than traditional mass spectrometry (i.e., nominal mass). Targeted analysis compared the retention time and precise mass of the unknown sample with a predetermined list of previously characterized compounds, including 19 synthetic cathinones, 40 synthetic cannabinoids, and 214 other common drugs of abuse.

Nontargeted analysis was used to assess for presence of compounds not included on the predetermined list. This analysis is possible because LC-TOF/MS measures accurate exact mass, which facilitates unambiguous assignment of potential formula matches to unknown samples. Toxicologists and public health staff generated a list of possible nephrotoxins: ochratoxins (A, B, C), pentynoic acid, and orellanine and orellanine. Ethylene glycol and melamine toxicity were considered inconsistent with clinical and pathological findings (e.g., no crystals observed). Analysis software was used to calculate each nephrotoxin’s exact mass, compare these with the unknown sample’s exact mass, and assess match probability and validity (MassHunter Qualitative Analysis; Agilent Technologies Inc., Santa Clara, California, USA).
 Matches were confirmed by comparing reference standards tested using the same techniques.

**Product traceback**

Given the ongoing risk associated with distribution of an apparently nephrotoxic product, public health personnel worked with law enforcement to determine where synthetic cannabinoid products were being sold. Law enforcement seized multiple synthetic cannabinoid products, which were subsequently tested to assess for presence of known synthetic cannabinoid compounds and other drugs of abuse.

**Results**

**Index case (Patient A)**

In August 2012, a previously healthy male aged 17 years presented to the emergency department after four days of flank pain, emesis, and oliguria that began after smoking a synthetic cannabinoid product called *Clown Loyal*. He denied fever, hematuria, headaches, and trauma, and reported regular marijuana use. He was hypertensive with a blood pressure [BP] of 152/79 mm Hg (95th percentile BP: 136/87 mm Hg) and exhibited bilateral costovertebral angle tenderness, but had neither edema nor rash. Initial blood urea nitrogen concentration (BUN) was 65 mg/dL (normal, 5–18 mg/dL) and serum creatinine concentration (Cr) was 9.1 mg/dL (normal, 0.5–1.0 mg/dL). Urinalysis and microscopy indicated more than 100 red blood cells/high-powered field, 2–5 white blood cells/high-powered field, trace proteinuria without cellular casts, and 1+ eosinophils. A renal ultrasound demonstrated bilaterally enlarged, hyperchoic kidneys. The patient received furosemide for oliguria and intravenous methylprednisolone (500 mg for 3 days) for suspected acute interstitial nephritis, followed by oral prednisone (30 mg twice daily). Common causes of AKI (obstruction, postinfectious immune complex deposition, autoimmune disease, systemic illness, dehydration, and exposure to known nephrotoxins) were excluded. A renal biopsy performed on hospital day 3 revealed acute tubular injury with mild interstitial nephritis.

Renal function improved with corticosteroid therapy and supportive care; serum creatinine concentration decreased to 1.7 mg/dL on hospital day 7. Patient A did not require hemodialysis and was discharged home on amlopidine, labetalol, and a 2-week corticosteroid taper. Hypertension resolved in 2 weeks, and his antihypertensive medications were discontinued. Blood pressure at 2-month follow-up was 124/54 mm Hg and serum creatinine concentration was 0.8 mg/dL. Urine protein-to-creatinine ratio at 9-month follow-up was 0.8 mg/dL (normal, <150–200 mg/day).

While searching for reports of synthetic cannabinoid-associated AKI, his nephrologist located a March 2012 *Epi-X* report from the Wyoming Department of Health describing four cases of AKI among males aged 15–21 years (median, 18.5 years) associated with smoking synthetic cannabinoids (unpublished *Epi-X* data, 2012). She contacted the Wyoming and Oregon Public Health Divisions. Retrospective review of Oregon Poison Center National Poison Data System records revealed a case with onset 1 month earlier (Patient B).

**Patient B**

In July 2012, a previously healthy male aged 15 years presented to an emergency department complaining of abdominal pain, nausea, and lower back discomfort lasting 3 days. He denied hematuria, dysuria, edema, or oliguria. He reported smoking marijuana and synthetic cannabinoid products during the previous months, but was elusive about the date of last exposure. He was euvolemic, but hypertensive with BP of 146/82 mm Hg (95th percentile BP: 131/83). His other vital signs and exam were unremarkable, except for mild epigastric tenderness. Electrolytes were normal, but BUN concentration was 48 mg/dL and serum creatinine concentration was 7.8 mg/dL. Urinalysis and microscopy revealed trace proteinuria without white or red blood cells or casts (2+ proteinuria was noted 1 day prior). A renal ultrasound revealed bilateral hyperechoic kidneys with poor corticomedullary differentiation. Initial care involved fluid management and oral prednisone (60 mg daily). As renal function worsened (BUN 61 mg/dL; Cr 9.1 mg/dL), hemodialysis was initiated on hospital day 2, and renal biopsy was performed on day 3. The biopsy indicated acute tubular necrosis with medullary peritubular capillaritis (Fig. 1). After a second hemodialysis treatment, fluid management, and abstention from synthetic cannabinoids after discharge, serum creatinine concentration improved without further intervention (0.9 mg/dL at 3 months; 0.8 mg/dL at 9 months), as did proteinuria. His blood pressure normalized from 126/78 mmHg at 3-month follow-up to 116/62 mmHg at 9 months.

**Case ascertainment**

Seven additional cases of AKI were identified, all having symptom onsets May–October 2012 (Table 1, Fig. 2). Of the nine total cases, six were identified from Oregon Poison Center calls (3 retrospective and 3 prospective), two by physician report alone, and one by patient chart review.

**Case summary**

All nine patients were males aged 15–27 years (median, 18 years). All nine resided in western Oregon or southwestern Washington, and reported smoking synthetic cannabinoids prior to onset of symptoms. Eight patients described their initial symptoms as acute onset of severe nausea, emesis, and back or abdominal pain (89%). In cases who recalled their last exposure, they reported symptom onset between approximately 30 min and 24 h (median: 8–12 h) after smoking a synthetic cannabinoid product. Cases 4 and 5 eluded repeated attempts to verify last exposure. One patient reported gross hematuria, and one presented with uremic encephalopathy (BUN 177 mg/dL). All required hospitalization (8 in Oregon, 1 in Washington); none died.
None of the nine patients had prior AKI and seven were previously healthy; one patient had pre-existing, untreated essential hypertension, and one had cyclic vomiting, later diagnosed as cannabinoid hyperemesis syndrome, which has not been associated with AKI. All patients had elevated peak systolic blood pressure (median, 154 mm Hg; range, 138–172 mm Hg). Initial BUN concentration ranged from 24 to 177 mg/dL (median, 42 mg/dL), and peaked at 28–177 mg/dL (median, 42 mg/dL). Initial serum creatinine concentration ranged from 2.6 to 17.7 mg/dL (median, 6.6 mg/dL); it peaked 2–7 days (median, 4 days) after symptom onset (median peak Cr, 7.9 mg/dL). Urinalysis revealed variable results: proteinuria (89%), white blood cells (44%), red blood cells (44%), eosinophils (11%), and hyaline casts (11%). Eight patients demonstrated leukocytosis (89%). Renal ultrasound performed on eight patients revealed a nonspecific increase in cortical echogenicity without hydronephrosis for seven (88%) patients.

All had normal serum creatine kinase levels; autoimmune and infectious diagnostic tests were negative. Recovery of renal function was apparent within 1 day after peak creatinine in the majority of patients (7; 78%). However, for two patients, peak creatinine persisted for 4 days, and recovery of renal function occurred only after the patients received corticosteroids (Patient A) or hemodialysis (Patient B). No alternative organic, pharmacologic, or toxic causes of AKI were identified, based on review of history and laboratory findings by investigators.

Patient interviews

Eight of the nine patients were contacted; six agreed to an interview. All six were habitual marijuana users; all but one (Patient A) admitted habitual synthetic cannabinoid product use with a variety of brands. Reasons for using synthetic cannabinoids included lower cost compared with marijuana, ease of purchase, perceived legality and safety, and the belief that use of synthetic cannabinoid would avoid detection on urine drug screening. Only Patient A reported being a first-time synthetic cannabinoid user. Patients reported purchase of synthetic cannabinoid products at different convenience stores, gas stations, tobacco shops, stores selling drug-related paraphernalia, or adult bookstores, either by themselves or by friends aged 18 years or above. No single synthetic cannabinoid brand explained all cases. Patients smoked synthetic cannabinoid products rolled into cigarettes or through a water pipe.

Patients included two sets of siblings who smoked together. Four patients had smoked the synthetic cannabinoid product with a total of five other contacts, none of whom reported illness to the cases. Patients reported smoking larger amounts (i.e., more tokes) of synthetic cannabinoid than their asymptomatic contacts (7–8 tokes vs. 1–2 tokes, respectively). Only one contact agreed to be interviewed; none of the contacts agreed to blood testing to assess renal function.

Clinical and product specimen testing

Synthetic cannabinoid products (n = 2) and clinical specimens (n = 9) were obtained from five patients (Table 2).
<table>
<thead>
<tr>
<th>Case no.</th>
<th>Patient Age, yrs</th>
<th>Product Brand Name</th>
<th>Initial Signs &amp; Symptoms</th>
<th>Last Use to Symptom Onset</th>
<th>Initial BUN/Cr, mg/dL</th>
<th>Peak BUN/Cr, mg/dL</th>
<th>Peak BP, mmHg</th>
<th>UA at Presentation</th>
<th>Renal Imaging</th>
<th>Treatment</th>
<th>Length of Stay, days</th>
<th>Follow-up BUN/Cr, mg/dL (time)</th>
<th>Follow-up Urinalysis (time)</th>
<th>Follow-up BP, mmHg (time)</th>
<th>Follow-up Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18</td>
<td>Unknown</td>
<td>Nausea, emesis, flank &amp; abdominal pain</td>
<td>&lt; 1 day</td>
<td>14/0.99</td>
<td>42/6.6</td>
<td>141/82</td>
<td>blood 1+, WBCs, protein 1+</td>
<td>U/S: Increased cortical echogenicity bilaterally</td>
<td>Fluid management</td>
<td>4</td>
<td>17/1.8 (3 mo)</td>
<td>small blood (3 mo)</td>
<td>13/066 (3 mo)</td>
<td>Chronic pain, drug-seeking</td>
</tr>
<tr>
<td>2</td>
<td>27</td>
<td>Mad Monkey or Clown Loyal</td>
<td>Flank pain, hematuria</td>
<td>14 days&lt;sup&gt;c&lt;/sup&gt;</td>
<td>24/4.3</td>
<td>29/4.7</td>
<td>157/106</td>
<td>blood 1+, no RBCs, protein 1+</td>
<td>U/S: Normal</td>
<td>Fluid management, anti-hypertensives</td>
<td>2</td>
<td>14/1.3 (4 days)</td>
<td>NA</td>
<td>131/86 (4 days)</td>
<td>Untreated essential hypertension</td>
</tr>
<tr>
<td>3</td>
<td>19</td>
<td>Jonny Clearwater (Caramel corn); Dr. Feelgood</td>
<td>Nausea, emesis, myalgia, fatigue, diaphoresis, flushed, oliguria</td>
<td>6.5 h</td>
<td>24/3.1</td>
<td>28/4.9</td>
<td>144/65</td>
<td>few WBCs, trace protein</td>
<td>U/S: Increased cortical echogenicity bilaterally</td>
<td>Fluid management</td>
<td>5</td>
<td>19/1.1 (12 days)</td>
<td>small LE, trace protein (12 days)</td>
<td>140/88 (12 days)</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>19</td>
<td>Unknown</td>
<td>Nausea, emesis, bilateral flank pain</td>
<td>14 days&lt;sup&gt;c&lt;/sup&gt;</td>
<td>32/2.6</td>
<td>32/2.6</td>
<td>138/81</td>
<td>WBCs</td>
<td>NC CT: Normal</td>
<td>Fluid management</td>
<td>4</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Sibling of Case 5</td>
</tr>
<tr>
<td>5</td>
<td>Pt B</td>
<td>Unknown</td>
<td>Nausea, emesis, abdominal &amp; flank pain, bradycardia, chest pain</td>
<td>14 days&lt;sup&gt;c&lt;/sup&gt;</td>
<td>48/7.8</td>
<td>61&lt;sup&gt;d&lt;/sup&gt;/9.1</td>
<td>146/82</td>
<td>trace protein</td>
<td>U/S: increased echogenicity bilaterally</td>
<td>Fluid management, anti-hypertensives, steroids, dialysis</td>
<td>6</td>
<td>15/0.8 (9 mo)</td>
<td>No protein (9 mo)</td>
<td>116/62 (9 mo)</td>
<td>Sibling of Case 4</td>
</tr>
<tr>
<td>6</td>
<td>Pt A</td>
<td>Clown Loyal</td>
<td>Nausea, emesis, flank pain</td>
<td>30 min</td>
<td>62/9.6</td>
<td>64/10.6</td>
<td>165/91</td>
<td>blood 4+, &gt; 100 RBC/hpf, trace protein, WBC 2–5, eosinophils 1+, protein 1+</td>
<td>U/S: Increased echogenicity bilaterally, bilateral enlarged kidneys</td>
<td>Fluid management</td>
<td>8</td>
<td>NA/0.8 (2 mo)</td>
<td>No protein (6 mo)</td>
<td>124/54 (2 mo)</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>18</td>
<td>Lava</td>
<td>Nausea, emesis, abdominal pain</td>
<td>7.5 h</td>
<td>20/1.6</td>
<td>37/5.5</td>
<td>164/60</td>
<td>blood 3+, no RBCs protein 2+</td>
<td>U/S: Increased cortical echogenicity; NC CT: Normal</td>
<td>Fluid management</td>
<td>8</td>
<td>NA/0.8 (2 mo)</td>
<td>NA</td>
<td>126/62 (3 mo)</td>
<td>Sibling of Case 8</td>
</tr>
<tr>
<td>8</td>
<td>18</td>
<td>Lava</td>
<td>Nausea, emesis, abdominal pain</td>
<td>7.5 h</td>
<td>48/6.3</td>
<td>65/9.6</td>
<td>163/77</td>
<td>blood 3+, no RBCs protein 2+</td>
<td>U/S: Increased cortical echogenicity; NC CT: Normal</td>
<td>Fluid management, diuretic</td>
<td>8</td>
<td>NA/0.8 (2 mo)</td>
<td>NA</td>
<td>120/54 (3 mo)</td>
<td>Sibling of Case 7; Lipase 773 mg/dL</td>
</tr>
<tr>
<td>9</td>
<td>26</td>
<td>Orgazmo (Pineapple)</td>
<td>Nausea, emesis, epigastric pain, headache, altered mental status</td>
<td>&lt; 1 day</td>
<td>177/17.7</td>
<td>177/17.7</td>
<td>172/83</td>
<td>blood 3+, WBCs, RBCs, protein 2+, hyaline casts</td>
<td>U/S: Increased echogenicity bilaterally; NC CT: Normal</td>
<td>Fluid management</td>
<td>4</td>
<td>20/1.5 (2 days)</td>
<td>NA</td>
<td>151/70 (2 days)</td>
<td>Probable cannabinoid hyper-emesis syndrome</td>
</tr>
</tbody>
</table>

BUN, Blood urea nitrogen; Cr, creatinine; BP, blood pressure; UA, urinalysis; WBC, white blood cells; U/S, renal ultrasound; RBC, red blood cells; NA, Not available; LE, leukocyte esterase; NC CT, non-contrast computed tomography; hpf, high-powered field
<sup>a</sup>Treated in Oregon and southwestern Washington hospitals.
<sup>b</sup>Time since discharge.
<sup>c</sup>Unable to verify by interview or unreliable historian.
<sup>d</sup>Peak BUN = 74 mg/dL coincided with Cr = 8.8 mg/dL.
Both products (different brand names) contained the synthetic cannabinoid (1-(5-fluoropentyl)-1H-indol-3-yl) (2,2,3,3-tetramethylcyclopropyl) methanone, also known as XLR-11, but no other tested synthetic cannabinoid, nephrotoxin, or drug of abuse. One patient had a clinical sample (serum) that was positive for synthetic cannabinoid. This sample was obtained within 2 days after exposure and tested positive for XLR-11 as well as one of its metabolites. Kidney biopsies tested negative for XLR-11 and other compounds in the testing panel. No additional synthetic cannabinoids or other drugs of abuse were identified in patient-associated product or clinical samples, except those prescribed (e.g., morphine, diazepam, and nordiazepam).

Product traceback and response

Law enforcement seized 14 different synthetic cannabinoid product brand and flavor combinations (not directly associated with cases) from reported purchase venues. Owners of these purchase venues incorrectly reported that the synthetic cannabinoid products they sold were legal. Toxicology testing determined that 3 of 14 (21%) contained XLR-11. Remaining samples contained 2 other synthetic cannabinoids: AM-2201 (n = 9) and UR-144 (n = 2). Product branding did not predict synthetic cannabinoid type.

A public broadcast featured the index patient, his nephrologist, and a public health official, and described the existence, illegality, and health risks associated with synthetic cannabinoid products. Law enforcement increased officer education and conducted synthetic cannabinoid product seizures. Communication with other poison control centers and the CDC alerted us to similar clusters nationwide.

Discussion

This case series demonstrates the emerging public health problem of synthetic cannabinoid abuse and the methods used to investigate novel toxicologic syndromes. Recent clusters of synthetic cannabinoid-associated AKI in multiple US states highlight the burgeoning use of synthetic cannabinoid and its potential toxicity. A total of 14 similar cases of synthetic cannabinoid-associated AKI were noted in Wyoming, Rhode Island, New York, Kansas, Oklahoma, and Alabama during February–December 2012. In Oregon, all nine affected patients were hospitalized, and one required hemodialysis. Conventional urine drug-assays might not detect synthetic cannabinoids, thus clinical suspicion should remain high in the setting of AKI. Collaborative investigation between medical toxicologists, other physicians, public health staff, and laboratorians identified a novel synthetic cannabinoid compound and highlighted the health risks associated with designer drugs.

Including our case series, approximately half of patients with synthetic cannabinoid-associated AKI reported in the literature were aged 18 years or below (11/23, 48%; median, 19 years; range, 15–33 years). According to one study, 11% of high school 12th graders and 4% of 8th graders reported using synthetic cannabinoid products during the prior 12 months. Populations wishing to avoid drug detection (e.g., parolees, employees in certain occupations, and military staff) might prefer synthetic cannabinoids because they are not detected through some urine drug-screening.

Table 2. Toxicological analysis of synthetic cannabinoid products and clinical samples from cases of acute kidney injury associated with synthetic cannabinoid use, Oregon, May–October, 2012, N = 9.

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Patient Age, yrs</th>
<th>Product used</th>
<th>Synthetic cannabinoids identified from product (mg/g)</th>
<th>Clinical specimen type</th>
<th>Interval between last use and sampling</th>
<th>Synthetic cannabinoids identified from clinical specimens (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>15</td>
<td>“Spice”</td>
<td>NA</td>
<td>Kidney biopsy</td>
<td>&gt;14 days</td>
<td>None detected</td>
</tr>
<tr>
<td>6</td>
<td>17</td>
<td>Clown Loyal</td>
<td>XLR-11 (92.1)</td>
<td>Kidney biopsy</td>
<td>7 days</td>
<td>None detected</td>
</tr>
<tr>
<td>7</td>
<td>18</td>
<td>Lava</td>
<td>XLR-11 (1.7)</td>
<td>Serum</td>
<td>9 days</td>
<td>None detected</td>
</tr>
<tr>
<td>8</td>
<td>18</td>
<td>Lava</td>
<td>XLR-11 (1.7)</td>
<td>Urine</td>
<td>48 h</td>
<td>Insufficient sample</td>
</tr>
<tr>
<td>9</td>
<td>26</td>
<td>Orgazmo</td>
<td>NA&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Serum</td>
<td>77 h</td>
<td>None detected</td>
</tr>
<tr>
<td></td>
<td>(Pineapple)</td>
<td></td>
<td></td>
<td>Serum</td>
<td>2 days</td>
<td>None detected</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Urine</td>
<td>2 days</td>
<td>None detected</td>
</tr>
</tbody>
</table>

NA, specimen not available
<sup>a</sup>Treated in Oregon and southwestern Washington hospitals.

Fig. 2. Acute Kidney Injury Among Synthetic Cannabinoid Users—Oregon, May–October, 2012, N = 9. Graph illustrates the onset of acute kidney injury, by month, among patients treated in Oregon and southwestern Washington. Each box equals one case.
assays.\textsuperscript{35} Similar to the patients we interviewed, young adults and adolescents appear to be unaware of the health risks associated with synthetic cannabinoids.

From a public health perspective, synthetic cannabinoid-associated AKI among healthy youth is concerning for several reasons. First, AKI is rare among persons aged 22–44 years, with an incidence of 0.6 cases/1,000 patient years.\textsuperscript{37} Second, the geographic range (several Oregon counties, multiple, non-contiguous states) and temporal distribution (February–December 2012) of AKI cases indicates that toxin exposure might have been widespread. Finally, despite normalization of kidney function among these nine patients, AKI secondary to any cause can predispose to renal insufficiency later in life. A meta-analysis assessing long-term renal outcomes among adult patients with and without AKI\textsuperscript{38} reported that patients with any history of AKI had an 8.8-fold higher risk for chronic kidney disease (CKD) and a 3.1-fold higher risk of developing end-stage renal disease, compared with patients without prior AKI.\textsuperscript{39} Of note, eight of nine cases in our series met criteria for moderate-to-severe kidney injury defined by RIFLE Stage F or AKIN Stage III.\textsuperscript{40} Healthcare personnel should be aware of the serious nephrotoxic effects associated with synthetic cannabinoid product use, treat the patient promptly, and contact local poison center and public health authorities.

Interestingly, we observed variable susceptibility to AKI among synthetic cannabinoid users and their contacts in this case series. It is possible that toxicity is dose-related: patients reported having smoked more synthetic cannabinoid than their asymptomatic contacts. Alternatively, non-standardized manufacturing processes increase the chance that these preparations contain uneven distribution of active compounds, exposing users to markedly different concentrations of drug.\textsuperscript{41} Toxicity might also be host-dependent because of variable predisposition to AKI. For example, males exhibit a more rapid decline in glomerular filtration rate with age than females, which might predispose males to AKI when exposed to a given nephrotoxin.\textsuperscript{42} Finally, the presence of two pairs of siblings in the case series, including identical twins, might indicate a common metabolic pathway (e.g., CYP genetic polymorphisms in cytochrome P450 enzymatic pathways) that made them more susceptible to a nephrotoxic compound present in the synthetic cannabinoid product.\textsuperscript{43}

Synthetic cannabinoid metabolism and potential toxicity might depend upon the drug’s chemical properties coupled with the host’s unique oxidative and conjugative metabolism. For example, Patton et al. showed markedly different metabolic profiles of human urine samples tested for JWH-018 and AM2201 oxidative and conjugative metabolites.\textsuperscript{44} Chimalakonda et al. studied the metabolism of synthetic cannabinoids using human recombinant P450 cytochrome enzymes and pooled human liver microsomes.\textsuperscript{45} They suggest that differences in hepatic cytochrome P450 enzymes might lead to impaired detoxification (e.g., decreased rate of oxidation or conjugation) or production of additional active metabolites, leading to prolonged exposure and, potentially, adverse effects. Evidence also suggests that glucuronic acid conjugation is necessary for urinary excretion of synthetic cannabinoid metabolites.\textsuperscript{46} A hereditary defect in conjugation might account for prolonged exposure to active metabolites, including a nephrotoxin, present in the smoked product. In our study, one case with persistent AKI had parent compound and metabolite present in a blood sample obtained > 40 h after ingestion. Prolonged serum levels have been observed by other investigators,\textsuperscript{47} although blood serum concentrations appear to peak within 30 min of inhalation.\textsuperscript{48} Finally, recent reviews suggest that differences in synthetic cannabinoids’ pharmacology (e.g., increased binding affinity at CB1 and CB2 receptors) and metabolism compared to delta-9-hydrocannabinol might explain observed toxicities.\textsuperscript{49} Further human studies are needed to elucidate the associations between synthetic cannabinoid active parent compound and metabolite levels, their elimination kinetics, and clinical symptoms.

In this investigation, innovative use of LC-TOF/MS detected a synthetic cannabinoid compound, XLR-11, and its predicted metabolites in clinical and product samples. XLR-11 is a fluorinated synthetic cannabinoid detected using toxicologic analysis of seized synthetic cannabinoid samples in the United States since early 2012, approximately the same time the first cluster of AKI was identified.\textsuperscript{50} XLR-11 is structurally similar to another synthetic cannabinoid, UR-144, which is a strong CB2 receptor agonist.\textsuperscript{51} The additional fluoride group on XLR-11 provides stability and prolongs half-life, a desirable effect for drug designers. Unlike CB1 receptors, CB2 receptors are widely distributed in peripheral tissues and narrowly distributed in the central nervous system.\textsuperscript{52,53} CB2 receptors are coupled with a G-protein receptor that inhibits adenylylate cyclase, and dysregulation of this enzyme is associated with organ system pathologies, including nephropathy.\textsuperscript{54} Evidence supporting XLR-11 as the nephrotoxin includes the presence of an endocannabinoid signaling system in rat and human kidneys; however, CB2 receptor expression has not been confirmed in kidney tissue.\textsuperscript{55–57} Finally, no other known nephrotoxins were identified among patients, and the existence of multiple clusters strengthens the epidemiologic link between AKI and synthetic cannabinoid products.

This study had limitations. Case finding might have been incomplete; our narrow case definition increased specificity at the cost of sensitivity. Although frank AKI in a young person is unusual and would have prompted a specialist referral, more mild cases might have remained undiagnosed. We cannot explicitly conclude that XLR-11 caused the observed AKI because identification of XLR-11 might simply reflect its distribution during this period. Heterogeneity of compounds in synthetic drugs is common, and product brands do not predict synthetic cannabinoid content.\textsuperscript{3,20,41} Metabolites of the synthetic cannabinoid compound, or combustion products created during smoking, might also be nephrotoxic. Other plausible etiologies include toxic plant material, solvent or flavor additive, or another as-yet-unidentified adulterant. By their nature, designer drugs are high-risk substances, and
reports of adverse effects continue to emerge, despite new federal laws banning their use and distribution. Effective collaboration between physicians, poison control centers, public health, laboratorians, and law enforcement is vital to recognizing, reporting, and responding to new toxicologic syndromes caused by synthetic cannabinoids. When evaluating a patient with symptoms indicative of toxin ingestion or an unexpected clinical syndrome, clinicians should inquire about substance abuse, including use of designer drugs. Prompt reporting and collection of urine and serum samples for testing can facilitate recognition of adverse effects related to designer drug use and promote rapid public health response.

Conclusion

We describe a cluster of AKI associated with smoking synthetic cannabinoid products among nine previously healthy adult males, including two pairs of brothers. XLR-11, a fluorinated tetramethylcyclopropyl ketone indole, was identified using LC-TOF/MS in two available product specimens, and one available clinical specimen. Hypotheses for the cause of AKI include direct toxicity from the synthetic cannabinoid, metabolic polymorphisms that predisposed to production of nephrotoxic metabolites among the cases, or as-yet-unidentified nephrotoxic contaminants.

Acknowledgments

We thank Matthew Friesen, BA (Univ of California, San Francisco) for his meticulous processing of clinical and drug samples; Jeff Moran, PhD (K2 Consortium, Alabama Dept of Health), Tracy Murphy, DVM (Wyoming Dept of Health), Michael Schwartz, MD, and John Devlin, MD (CDC, National Center for Environmental Health/Agency for Toxic Substances and Disease Registry), and David Farrer, PhD (Oregon Public Health Division) for their invaluable consultation about synthetic cannabinoid toxicology; Alan Melnick, MD and Josh VanOtterloo, MPH (Public Health Department, Clark County, WA) for their assistance with patient investigation in Washington; Dan Sudakin, MD (Oregon State University) and Dan Petersen, PhD (University of California, Davis) for their consultation about plant nephrotoxins; Katrina Hedberg, MD, MPH, and Sean Schafer, MD, MPH (Oregon Public Health Division), for their assistance with initial study design and manuscript composition; Portland Drug Enforcement Agency (Multnomah County, Oregon) and Douglas County Inter-agency Narcotics Team (Douglas County, Oregon) for their collaboration; as well as patients and their families for trusting us with their stories.

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official positions of the Oregon Public Health Division, University of California, or the Centers for Disease Control and Prevention.

Financial Disclosure: Dr. Buser was supported by the Epidemic Intelligence Service Fellowship through the Centers for Disease Control and Prevention. The remaining authors have no financial relationships relevant to this article to disclose.

Role of the Sponsor: The Centers for Disease Control and Prevention, Oregon Public Health Division, University of California, San Francisco, Douglas County Public Health, and Oregon Health & Sciences University had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Declaration of interest

The authors report no declarations of interest. The authors alone are responsible for the content and writing of the paper.

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