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Case report

Synthetic cannabinoid induced acute respiratory depression: Case series and literature review

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ABSTRACT

Synthetic Cannabinoids are a street drug that is widely attainable and cheap compared to natural cannabis, and has variable potency and unpredictable effects with no commercially available diagnostic test to confirm its presence. Similar to natural cannabis, Synthetic Cannabinoid intoxication can present in several ways with the most common emergency room presentations to be of neurologic and psychiatric manifestation. The respiratory depressive effect of Synthetic Cannabinoids has not been well documented in medical literature.

We report four patients admitted in the Intensive Care Unit with acute respiratory failure necessitating endotracheal intubation after use of Synthetic Cannabinoid. All patients had a reversal of respiratory failure in less than 24 h, three patients had a complicated course due to aspiration pneumonia. All four patients exhibited aggressive behavior, with two of them diagnosed with Bipolar Disorder and Cocaine Use Disorder.

The effect of Synthetic Cannabinoids in peripheral receptors such as chemoreceptors and baroreceptors can increase bronchial airway resistance. It is postulated that CB1 receptor stimulation could be one of the possible mechanisms of synthetic cannabinoid-induced respiratory depression. Chemical gases released after its inhalation may also cause damage to the bronchiolar epithelium and has the potential to disrupt the protective surfactant layer in the alveoli, which then could interfere with effective gas exchange leading to hypoxia and acidosis. The stimulation of CB1 receptors have a series of downstream signaling effects in the G protein-coupled pathway and mitogen-activated protein kinase (MAPK) pathway, causing suppression of both excitatory and inhibitory neuronal activity. The aforementioned molecular changes in the central nervous system after CB1 receptor stimulation could impact respiration.

The use of Synthetic Cannabinoids can cause respiratory depression in individuals without an underlying pulmonary disease and adds to the growing number of literature about the presentation and debilitating adverse events from its consumption. Although there is no specific toxidrome associated with it, clinicians should have a high index of suspicion with its use especially in patients presenting with a history of drug overdose.

1. Introduction

Synthetic cannabinoid-related emergency department visits in the northeast region of the United States have been steadily increasing, with more than 1200 emergency room encounters occurring every month since July 2016 [1–3]. Males account for 90% of these visits with a median age of 37. Most of the patients are residents of shelters and individuals with psychiatric illnesses [1]. It is reasonable to project that this current epidemic will slowly affect every state as its use becomes more rampant.

In the advent of marijuana legalization in some states such as Colorado, California, Maine, and Nevada, consumption of synthetic cannabinoids has been very appealing due to its availability and cheaper price compared to its natural counterpart. It is usually purchased as pulverized herbs to be ingested, used as incense or rolled with natural marijuana to be smoked. They are cleverly packaged as well to entice consumers who would not otherwise consume cannabis [4,5].

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There are more than 50 types of synthetic cannabinoids known and they are often mixed in every packet, making each packet unique with variable potency and unpredictable effects [6]. Currently, a synthetic cannabinoid Enzyme Linked ImmunoSorbent Assay (ELISA) test was developed as a presumptive initial test, which for forensic purposes has to be confirmed through chromatography and mass spectrometry technique. These tests can only screen a handful of the metabolites and are not commercially available [7].

The use of synthetic cannabinoid is associated with variable but surely debilitating adverse events [4]. Similar to natural cannabis, being intoxicated with synthetic cannabinoid can present in a number of ways, with the most common symptomatic presentations as nausea, vomiting, anxiety, agitation, paranoid ideations and psychosis [8,9]. Case reports have been published with outcomes of seizures, encephalopathy, acute stroke, hypertension, cardiotoxicity, pneumonia, diffuse alveolar hemorrhage, severe lung injury and consequences such as death from coronary ischemic event and arrhythmias [10,11]. The depressive effects of the synthetic cannabinoid in the respiratory system have not been thoroughly described, with just one published case report in 2012, long before it has been identified as an impending epidemic [4]. We present four cases of synthetic cannabinoid-induced respiratory depression necessitating endotracheal intubation for airway support. All of the cases were encountered during a span of one week in the intensive care unit of a city hospital. This is during a week when multiple hospitals are receiving drug intoxications from a new street drug that cannot be detected by a standard toxicology test [12].

2. Methods

We prospectively gathered data on patients who were admitted to the intensive care unit during a one-week span of time. A diagnosis of synthetic cannabinoid-induced acute respiratory failure was made in patients presenting with signs and symptoms requiring an advanced airway, specifically an endotracheal tube. We noted that while there is no diagnostic test that will confirm the use of synthetic cannabinoid, a history of its use a few hours prior to presentation as stated by the patient or emergency medical personnel is sufficient.

The patients in the present case series all have in common (see Tables 1 and 2):

Table 1
Arterial blood gas results on admission and after 24-h with the reference ranges.

ARTERIAL BLOOD GAS									
Test	Patient 1		Patient 2		Patient 3		Patient 4		Reference Range
	On Admission	After 24 hours	On Admission	After 24 hours	On Admission	After 24 hours	On Admission	After 24 hours	
pH	7.10	7.41	6.98	7.42	7.198	7.40	7.14	7.35	7.35–7.45
pCO2	88.2 mmHg	38.1 mmHg	57.9 mmHg	36.3 mmHg	70.3 mmHg	46.7 mmHg	84.0 mmHg	44.7 mmHg	35-45 mmHg
pO2	78.0 mmHg	132.0 mmHg	58.9 mmHg	92.0 mmHg	107.0 mmHg	71.0 mmHg	83.1 mmHg	59.0 mmHg	80-105 mmHg
sO2	80%	99%	69.10%	97%	96.15	94%	92%	95%	95-98%

Table 2
Summary of serum and urine test results on admission with the reference ranges.

Test	Patient 1	Patient 2	Patient 3	Patient 4	Reference range
Complete Blood Count (CBC)					
Hemoglobin	13.7 g/dL	14.1 g/dL	13 g/dL	14.8 g/dL	14-18 g/dL
Hematocrit	41%	39.40%	39.70%	41.90%	40-54%
White cell count	10.1 K/uL	25.1 K/uL	11 K/uL	6.2 K/uL	4.5–11.5 K/uL
Platelet	228 K/uL	434 K/uL	287 K/uL	429 K/uL	150-450 K/uL
Neutrophil	4.3 K/uL	14.9 K/uL	5.3 K/uL	2.5 K/uL	1.9–7.7 K/uL
Lymphocyte	4.1 K/uL	7.7 K/uL	6.9 K/uL	2.3 K/uL	0.7–5.0 K/uL
Monocyte	0.8 K/uL	2.2 K/uL	0.7 K/uL	0.9 K/uL	0.16–1.25 K/uL
Eosinophil	0.8 K/uL	0.2 K/uL	0.0 K/uL	0.5 K/uL	0.0–0.8 K/uL
Basophil	0.1 K/uL	0.1 K/uL	0.0 K/uL	0.1 K/uL	0.0–1.0 K/uL
Chemistry					
Sodium	139 mmol/L	135 mmol/L	146 mmol/L	135 mmol/L	136-145 mmol/L
Potassium	3.51 mmol/L	4.45 mmol/L	4.06 mmol/L	3.72 mmol/L	3.5–5.1 mmol/L
Chloride	104 mmol/L	99 mmol/L	107 mmol/L	103 mmol/L	98-107 mmol/L
Bicarbonate	28 mmol/L	14 mmol/L	31 mmol/L	22 mmol/L	21-32 mmol/L
BUN	18 mg/dL	13 mg/dL	11 mg/dL	14 mg/dL	7-18 mg/dL
Creatinine	1.1 mg/dL	1.8 mg/dL	0.7 mg/dL	0.8 mg/dL	0.44–1.10 mg/dL
Glucose	103 mg/dL	233 mg/dL	127 mg/dL	111 mg/dL	70-99 mg/dL
Magnesium	1.8 mg/dL	2.4 mg/dL	2.2 mg/dL	2.0 mg/dL	1.8–2.4 mg/dL
Phosphorus	4.1 mg/dL	2.6 mg/dL	5.5 mg/dL	5.0 mg/dL	2.5–4.9 mg/dL
Other Tests					
Serum Alcohol	<3.0 mg/dL	<3.0 mg/dL	2 mg/dL	<3.0 mg/dL	<5 mg/dL
Creatine Kinase	135 Units/L	1163 Units/L	233 Units/L	364 Units/L	39-308 Units/L
Urine Toxicology					
Opiates	positive	negative	negative	negative	<300 ng/mL
Barbiturates	negative	negative	negative	negative	<200 ng/mL
Cocaine	negative	negative	positive	negative	<300 ng/mL
Benzodiazepines	positive	negative	negative	negative	<200 ng/mL
Methadone	negative	negative	negative	negative	<300 ng/mL
Amphetamines	negative	negative	negative	negative	<1000 mg/dL
Cannabinoid	negative	positive	negative	positive	<50 ng/mL
Phencyclidine	negative	negative	negative	negative	negative

1. Use of synthetic cannabinoid before presenting to the emergency department.
2. Development of acute respiratory failure with subsequent endotracheal intubation.
3. Reversal of acute respiratory failure.
4. The absence of concomitant pulmonary disease.
5. Featured aggressive, combative, agitated and restless behavior.

The use of synthetic cannabinoid remains a clinical diagnosis. However, work up for the following cases relied on widely available tests to rule out other causes of acute respiratory failure. In each situation, each patient received a chest radiograph, urine toxicology, arterial blood gas, trending of serum chemistries, bicarbonate, electrolytes and a complete blood count. The diagnosis of synthetic cannabinoid-induced acute respiratory failure is confirmed either through reports by emergency medical services that patient was found with packets of the synthetic cannabinoid in their pockets, saw their consumption of the substance or when patients report their use upon return to baseline mental status.

3. Case presentation

3.1. Patient 1

The patient is a 27-year-old male of Hispanic ethnicity found in the courtyard of a homeless shelter by emergency medical personnel. He was found to be in significant respiratory distress and received endotracheal intubation while in the field. In addition, EMS administered naloxone which did not produce a response. He was transported to our emergency department for further care. The arterial blood gas result in the ED showed acute respiratory acidosis while other serum laboratory tests showed unremarkable results. Urine toxicology was obtained which showed positive for the use of opiates and benzodiazepines. The chest radiograph that was performed on initial presentation did not show any significant results. However, subsequent imaging showed a developing right lower lobe consolidation and atelectasis with an associated small pleural effusion. The patient received sedation and analgesia with concurrent supportive care. He gradually regained full faculties the following morning with difficulty in keeping him calm. The patient exhibited combative and aggressive behavior which resulted into self-extubation. He signed out against medical advice after evaluation by Psychiatry that he has the capacity to decide what he wants with his care. He conveyed that he smoked synthetic cannabinoids before experiencing shortness of breath. The patient was lost to follow up and the long-term outcome is unknown.

3.2. Patient 2

The patient is a 28-year-old African American male with Bipolar Disorder who was brought in by emergency medical personnel due to a seizure episode while in his homeless shelter. He had a witnessed seizure while in the emergency department with development of fever, altered mental status and inability to protect his airway prompting endotracheal intubation. While awaiting transfer to the intensive care unit, he received additional sedation due to restlessness. He was eventually transferred to the adult intensive care unit where he received care. The arterial blood gas showed acute respiratory acidosis together with serum laboratory tests which revealed lactic acidosis, rhabdomyolysis, and acute kidney injury. His Chest radiograph is unremarkable. The patient regained capability to protect his airway and was successfully extubated with the resolution of acute respiratory acidosis the following morning. The patient was irritable and fought with medical staff regarding his care and demanded to be discharged. However, he developed fever and was evaluated by Psychiatry to have no decisional capacity. The patient stayed and received additional treatment for aspiration pneumonia. He was discharged after staying in the hospital for 3 days and confessed that he inhaled synthetic cannabinoids and ingested marijuana seeds before having a seizure. The patient was given a referral to follow up with chemical dependency clinic. Unfortunately, he never followed up and has never been seen in the facility since.

3.3. Patient 3

The patient is a 55-year-old African American female with a history of Cocaine use brought in by emergency medical personnel due to seizures. She was intubated upon arrival to the emergency department due to the development of stupor with concomitant oxygen desaturation with arterial blood gas showing acute respiratory acidosis. Additional information from the emergency medical personnel stated that the patient was picked up from the street while seen smoking the synthetic cannabinoid followed by seizures. All other serum laboratory results were unremarkable during that time with negative urine toxicology for any detectable substances. The chest radiograph did not show any infiltrates, consolidations or any acute diseases either. Prior to the patient's transfer from the emergency department to the intensive care unit, she regained full faculties, exhibited agitation and extubated herself. Instead, she was placed in bi-level positive airway pressure and was monitored in the intensive care unit for 24 hours. She was subsequently transferred to the medicine floors after significant clinical improvement and resolution of acute respiratory acidosis. The patient had an uneventful medicine floor course and was discharged the same day with recommendations to follow up with medicine and neurology clinic. She was never started on any antiseizure medication when she was seen in neurology clinic a week after discharge due to the absence of seizure recurrence. The patient never showed up in her scheduled medicine clinic appointment and was lost to follow up.

3.4. Patient 4

The patient is a 30-year-old African American male brought in after he was found unresponsive while lying in the street. Upon arrival of EMS, they have found that the patient was hypoventilating at 4 to 6 breaths per minute and in a pool of vomitus. A dose of Naloxone was administered which was ineffective prompting subsequent intubation while in the field. A bystander reported to EMS that the patient has seen earlier smoking synthetic cannabinoid. The report mentioned that the intoxicated patient was aggressively picking a fight prior to being found unresponsive in the street. His arterial blood gas upon presentation showed acute respiratory acidosis with unremarkable serum laboratory tests and chest radiograph. The patient was admitted to the intensive care unit and his respiratory status improved upon optimization of mechanical ventilation. On the third day of management, the patient developed a fever of 103° Fahrenheit accompanied by a new right lower lobe consolidation on chest radiograph prompting the start of antibiotic coverage for Aspiration pneumonia. After 5 days, he improved significantly with normalization of arterial blood gases and was extubated. The patient was transferred to the medicine floor with the continuation of the antibiotic course. He was discharged with a scheduled outpatient follow up to chemical dependency clinic. The patient mentioned that he had been smoking synthetic cannabinoids before losing consciousness and being found by EMS. He never showed up in his scheduled clinic appointment and was lost to follow up with unknown long-term outcomes.

4. Discussion

In order to recognize the effects of synthetic cannabinoids in respiration, it is vital to understand the role and distribution of the cannabinoid receptors and the different molecules that act as ligands to them. The cannabinoid receptors are mainly found in the central nervous system and immune system with CB1 receptors being predominant in the brain's hippocampus, basal ganglia, cortex, amygdala, and cerebellum, while CB2 receptors actively interact peripherally in the immune system [13]. CB1 and CB2 receptors may also modulate non-cannabinoid receptors such as muscarinic, nicotinic, opioid and serotogenic receptors leading to a multitude of physiological effects [14].

After the discovery of the cannabinoid receptors, several studies in the pharmaceutical industry were conducted to develop molecules that could act as ligands for these receptors [15]. They were initially developed to investigate possible therapeutic effects and to further the research on endocannabinoid receptor systems [16]. These cannabinoid ligands are categorized into five distinct types based on their molecular structure and are termed classical, non-classical or cyclohexylphenols, naphthoylindoles, eicosanoids and the unclassified group respectively [17–20].

These cannabinoids vary in their potency, efficacy, affinity, selectivity, metabolic and molecular activity. They vary from acting as a full agonist, partial agonist, and inverse agonist compared to the partial agonist activity of natural marijuana which has the tetrahydrocannabinol (THC) structure [21–23]. The majority of their metabolites also have longer half-lives. Notable among them is the JWH-018 which retains its metabolic activity in the CB1 receptor explaining the increased prevalence of adverse events with the JWH-018 compared to natural cannabis. In addition, it also has a four-fold affinity to the CB1 receptor and a ten-fold affinity to the CB2 receptor [24].

The effect of Synthetic Cannabinoids in respiration has not been extensively detailed in humans and likely involves multiple mechanisms of action. Research involving rats have demonstrated marked respiratory depression, characterized by a decrease in respiratory rate, hypoxia, hypercapnia and arterial blood gas acidosis. Synthetic Cannabinoid effect on peripheral receptors such as chemoreceptors and baroreceptors, can increase bronchial airway resistance postulating that CB1 receptor stimulation could be one of the possible mechanism of synthetic cannabinoid-induced respiratory depression [25]. Chemical gases released after inhalation of Synthetic Cannabinoids may also cause damage to the bronchiolar epithelium [16]. It also has the potential to disrupt the protective surfactant layer in the alveoli and interfere with the effective gas exchange, leading to hypoxia and acidosis manifesting as acute respiratory distress which could progress to respiratory failure.

The stimulation of CB1 receptors has a series of downstream signaling effects, notably the G protein-coupled pathways and mitogen-activated protein kinase (MAPK) pathway. The CB1 receptor is particularly linked to the $G_{i/o}$, which upon stimulation inhibits adenylyl cyclase and decreases cellular cyclic adenosine monophosphate (cAMP) levels. As CB1 receptors are found in both glutaminergic and GABAergic terminals, their stimulation, theoretically can suppress excitatory and inhibitory neuronal activity. On the other hand, the MAPK pathway is specifically linked to synthetic cannabinoid agonist activity. This results in the phosphorylation of nuclear transcription factors, which in turn impacts cellular transcription, translation, motility, shape, proliferation, and differentiation. In addition to these pathways, prolonged phosphorylation of CB1 receptor leads to desensitization and internalization. These molecular changes that occur in the central nervous system after CB1 receptor stimulation could impact respiration [18].

The drug concentration of synthetic cannabinoids to produce the aforementioned effects were observed in an in vivo study involving mice, which noted that analgesia is observed at a median effective dose (ED50) of 0.09 mg/kg and hypothermia was recorded at doses of 1.47 mg/kg. In a separate study involving rats, a drug concentration of 10 mg/kg decreased the rate of breathing of animal subjects with subsequent demise [26].

A common misconception regarding the use of synthetic cannabinoids is the absence of a diagnostic test to confirm its use. In a study done in 2011, the researchers determined that the structure of JWH-018 metabolites can be excreted in the urine, which therefore can be used to detect its presence using a urine sample [27]. Another study done in the same year showed that several monohydroxylated metabolites, a carboxy metabolite, a dihydroxy metabolite and a trihydroxy metabolite can be detected in oral fluid and urine samples provided by human subjects after smoking synthetic cannabinoid [28]. These data propose that mass spectroscopy using saliva and urine could be used to confirm the recent use of some synthetic cannabinoids. However, this technology is not commercially available at the moment and several types of synthetic cannabinoids are formulated as of this day with unknown pharmacokinetics and pharmacodynamics [29].

5. Conclusion

This case series present that synthetic cannabinoids can cause respiratory depression in patients without an underlying pulmonary disease and adds to the growing number of literature about the presentation and debilitating adverse events from its consumption. Although there is no specific toxidrome associated with its use, clinicians should have a high index of suspicion in patients presenting with a history of a drug overdose. Further studies are needed to investigate the effects of synthetic cannabinoids to behavioral pathways in the brain and to address the molecular interaction of other unknown types and their vehicles with receptors to subsequently predict and learn their pharmacokinetics and pharmacodynamics.

Competing interests

The authors have no financial relationships or competing interests to declare.

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