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Intranasal naloxone to treat suspected synthetic cannabinoid overdose: A case report and literature review

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Abstract

Synthetic cannabinoids (SCs), such as K2 or spice, are potent, intoxicating, laboratory-produced compounds designed to mimic Δ9-tetrahydrocannabinol (Δ9-THC). Some SCs are full agonists that bind to cannabinoid receptors in the endocannabinoid system with significantly higher affinity than Δ9-THC, often causing more intense and unpredictable effects, including cardiovascular, respiratory, and neuropsychiatric complications. Due to their modifiable chemical structures, new SC variants are commonly created and can evade detection on standard toxicology screens, complicating diagnosis and treatment. A 43-year-old male with schizoaffective disorder and polysubstance dependence presented with mental status changes and respiratory depression following suspected SC use with K2. Symptoms improved with intranasal naloxone despite negative toxicology screens for opioids and known SCs. The patient later admitted to ongoing K2 use. A unit search revealed leafy substances though confirmatory testing was negative. This case raises important considerations about the limitations of routine toxicology screening and the risk of SC adulteration with opioids or other undetected substances. The patient's repeated clinical improvement following naloxone suggests either opioid contamination or functional interactions between cannabinoid and opioid receptors. Preclinical evidence supports the existence of CB1-opioid receptor cross talk, offering a possible explanation for naloxone's effectiveness in SC-related toxicity. Clinicians should consider naloxone in cases of suspected SC overdose even without confirmed opioid exposure. Naloxone's safety profile and rapid onset make it an additional tool in managing undifferentiated overdose presentations. Further research is needed to delineate the mechanism behind naloxone's potential effectiveness in SC-related toxicity.

Keywords: synthetic cannabinoids, toxicology, overdose, naloxone, opioids

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Background

Synthetic cannabinoids (SCs) are a diverse class of laboratory-produced, intoxicating compounds that are potent agonists in the endocannabinoid system (ECS),[1,2] Originally developed to study ECS signaling and therapeutic applications, SCs were later developed and produced by clandestine chemists to create illicit products marketed as designer drugs under names such as K2 and spice.[3] Because early SCs could avoid detection on standard cannabinoid screening tests, SCs gained popularity in the early 2000s as "legal" highs.[3] Despite efforts to classify many SCs as controlled substances, their frequent structural modifications continue to outpace legal regulation and standard toxicology screening.[3] Recent data from the National Survey on Drug Use and Health shows SC use in the general US population is rare and increasing with the past-year prevalence rising from 0.17% in 2021 to 0.26% in 2023.[4]

SCs act in the mammalian ECS. The ECS is a complex neuromodulatory system that plays a vital role in physiological balance, particularly in the central nervous system (CNS), where it regulates neurotransmission, CNS development, neurogenesis, neuroprotection, motor control, memory, cognition, learning, stress, emotional responses, reward, and motivated behavior.[5,6] The ECS also influences the immune, endocrine, digestive, and reproductive systems.[5,6]

The ECS consists of endogenous cannabinoids (endocannabinoids), their receptors, and the enzymes responsible for synthesizing and degrading endocannabinoids.[5,6] Key endocannabinoids, such as anandamide and 2-arachiodonoylglycerol, are synthesized from the lipid component of cell membranes in response to classic neurotransmission and are rapidly degraded after exerting their effects.[5,6] Classic endocannabinoid receptors include cannabinoid receptor 1 (CB1) and cannabinoid receptor 2, which are both G-coupled protein receptors (GCPRs).[5,6] CB1 receptors are the most common GCPRs in the CNS and important targets for endogenous and SCs.

Δ9-Tetrahydrocannabinol (Δ9-THC), the primary intoxicating cannabinoid in cannabis, is a partial agonist at CB1 receptors.[5,6] When Δ9-THC binds to CB1 receptors, neurotransmission is inhibited.[5,6] This inhibition can have complex downstream effects depending on whether excitatory or inhibitory neurons are involved and on specific neural circuits engaged.[5,6]

In contrast, many SCs are full CB1 receptor agonists with higher binding affinities than Δ9-THC. SC can produce pharmacologic effects 2 to 100 times more potent than Δ9-THC.[2,7] SCs' heightened potency and variable pharmacologic profiles can cause unpredictable effects ranging from mild euphoria to psychiatric and medical emergencies.[2] Adverse effects include agitation, anxiety, paranoia, hallucinations, psychosis, seizures, and loss of consciousness as well as cardiovascular toxicity such as tachycardia, hypertension, myocardial infarction, and sudden cardiac death.[2] Other reported toxicities include acute kidney injury, hepatic failure, hemorrhage, and coagulopathies due to contamination with brodifacoum, a long-acting anticoagulant rodenticide.[2] Chronic SC use is associated with an increased risk of persistent psychosis, cognitive deficits, and neurodevelopmental disorders, especially in adolescents.[3]

Respiratory failure, though uncommon with cannabis, is a concerning toxic effect reported with SC overdose.[8] A 2022 case series documented instances of profound central respiratory depression after SC exposure, suggesting that SCs may result in an exaggerated CB1 receptor response or off-target effects in brainstem respiratory centers.[8] Naloxone, a high-affinity mu-opioid antagonist, is FDA-approved to reverse opioid-induced respiratory depression. Although primarily used for opioid toxicity, there are case reports suggesting naloxone's potential effects on cannabinoid-related intoxication.[9] One proposed mechanism involves GCPR cross talk between the ECS and opioid systems.[10] CB1 receptors are known to heterodimerize with other receptor types, including opioid receptors, forming novel functional units that can physically interact and influence each other's activity.[10] This cross talk between the ECS and opioid system may explain why naloxone, despite targeting opioid receptors, may indirectly mitigate SC-induced symptoms.[10]

Preclinical studies support this hypothesis. In animal models, naloxone induces withdrawal-like symptoms in subjects that are dependent on Δ9-THC, suggesting that there is a shared pathway of action between the ECS and opioid system.[11] The complexity of SC pharmacology and its interaction with other systems underscores the need for vigilance in clinical care.

This case report explores a patient with suspected SC toxicity and respiratory depression who improved with intranasal naloxone administration. Although this patient may have responded to naloxone due to undetectable opioid-like substances in the suspected substance, this case raises important questions about the ECS-opioid system interplay and evolving challenges in managing SC toxicity.

Case Report

A 43-year-old male, who is a long-term resident of an inpatient state psychiatric facility, was seen emergently for a suspected drug overdose. Psychiatric diagnoses included schizoaffective disorder, bipolar type, and polysubstance dependence (cannabis, opioids, stimulants, and hallucinogens). Before his admission several years prior, the patient reported daily cannabis consumption. The patient was stable on bupropion XL 150 mg by mouth once daily, olanzapine 15 mg by mouth twice daily, quetiapine 400 mg by mouth at bedtime, and sertraline 100 mg by mouth in the morning.

On day 1, the morning of the suspected overdose, nursing observed the patient pacing. Around 7:45 AM, the patient sat in a chair, began snoring loudly, was difficult to arouse, and drifted in and out of alertness. The patient responded to the nurse's name and his name but not the environment. His pupils were constricted and nondilating; he could not keep his eyes open or head upright. Initial vitals were unremarkable except for a heart rate of 131 beats per minute (bpm). Repeated vitals were still notable for an elevated heart rate of 124 bpm and an oxygen saturation dropping from 97% to 85% on room air. The psychiatrist ordered naloxone 4 mg intranasally. Minutes later, the patient was more alert and responsive. He was

transferred to the emergency department at 8:40 AM. During the emergency department visit, his urine toxicology screen was negative for amphetamines, 3,4-methylenedioxymethamphetamine (MDMA), barbiturates, benzodiazepines, Δ9-THC, cocaine, codeine, morphine, and methadone. He returned to the state hospital at 3:06 PM and was transferred to a higher security level unit with daily contraband searches. Although the contraband search of his previous unit was unremarkable, staff members received reports that the patient used K2 before the incident.

On day 2, patients reported the presence of K2 circulating within the hospital; however, contraband searches conducted across units yielded negative results. On day 5, slurred speech and somnolence were observed in the patient at 1:20 PM. Vital sign abnormalities included an elevated blood pressure of 142/93 mmHg and a heart rate of 112 bpm. The patient refused urine drug testing. That evening, there were reports of the smell of smoke on the unit at 10:40 PM, but a unit search was unremarkable. On day 6, a dried, crushed, greenish brown leafy substance was found during a unit search at 9:38 AM and given to authorities. The patient's urine toxicology sample from 4:05 PM later that afternoon was negative for amphetamines, benzodiazepines, alcohol, buprenorphine, cocaine, 6-acetylmorphine, cannabis metabolites, MDMA, codeine, hydrocodone, hydromorphone, norhydrocodone, oxycodone, noroxycodone, oxymorphone, and 12 different SC compounds.

Three days later, on day 9 at 2:00 AM, the patient went into the bathroom for 30 to 40 minutes with a strong odor present inside as he exited. The patient was confused, lethargic, and holding the sink for support with an unsteady gait. Vitals were unremarkable except for an elevated heart rate of 118 bpm. After another suspected overdose, he was transferred out to the emergency department by emergency medical services (EMS) at 3:27 AM. His mental status improved after paramedics administered intranasal naloxone. His urine toxicology screen in the emergency department was negative for MDMA, barbiturates, benzodiazepines, Δ9-THC, cocaine, codeine, morphine, and methadone but positive for amphetamines.

The patient returned from the emergency department on day 9 at 7:35 AM. At 9:22 AM, the patient was again found with altered mental status changes after being in the bathroom with another patient. A dried, crushed, greenish brown leafy substance was recovered in his room. During the interview, the patient reported to the psychiatrist that he had been smoking and ingesting K2 for the past few weeks. Naltrexone 50 mg by mouth daily was initiated but was discontinued 3 months later due to the patient's refusal. Other restrictions were put in place to limit drug use.

Discussion

SCs, marketed as K2 or spice, pose a significant public health concern due to their widespread use and unpredictable clinical effects.[1] Continuous modification of SC structures complicates toxicology testing, diagnosis, and treatment.[12] This case of naloxone-responsive respiratory depression following suspected K2 ingestion highlights critical issues in managing SC toxicity.

Naloxone, a high-affinity mu-opioid receptor antagonist, should be promptly administered in any case of suspected overdose regardless of the presumed causative agent.[13] Naloxone's role in SC toxicity remains poorly understood; however, emerging evidence suggests a complex interplay between the endocannabinoid and opioid systems. Although the exact mechanism remains unclear, naloxone's ability to reverse respiratory depression in this case reinforces its importance as a first-line intervention even in scenarios in which opioid toxicity is in question.

As SCs evolve, the literature surrounding their clinical effects and treatment strategies will expand. This case is a reminder that clinicians will likely encounter increasingly diverse presentations of SC toxicity. The rapid pace of SC development highlights the need for ongoing research to elucidate their pharmacologic properties, toxicologic profiles, and potential interactions with other receptor systems.[3]

Diagnostic Challenges with Synthetic Cannabinoids

The inability to reliably confirm exposure is a major challenge in managing SC toxicity.[2,3] Structural modifications allow toxicology samples to bypass legal restrictions and standard toxicology screens.[3] Clinicians often depend on patient, bystander, or EMS reports, which may be incomplete or inaccurate. Although this patient's reported K2 use could not be confirmed analytically, the clinical presentation of respiratory depression, tachycardia, and hypertension as well as responding to naloxone in the presence of a K2-like substance suggest possible SC ingestion with opioid-like effects. Notably, toxicology screening in this case did not include fentanyl testing, limiting definitive conclusions. Although SC use couldn't be confirmed, it's important to mention that no fentanyl-positive urine drug screens were reported at the state psychiatric hospital in the year prior to the incident. During this period, 567 general urine drug screens were collected; 378 included fentanyl testing, and all were negative.

Given the lack of definitive testing, clinicians must maintain a high index of suspicion for SC exposure, particularly in patients presenting with unexplained altered mental

status, respiratory depression, or atypical toxicologic features. As newer SC compounds emerge, advancements in diagnostic tools will be critical to improving the detection and understanding of these substances. It is also critical to recognize that substances sold as K2 may be adulterated with opioids. Although there is a theoretical basis for cross talk between opioid and cannabinoid receptors, the observed efficacy of naloxone in this case may be more plausibly attributed to opioid contamination.[10] Variability in urine drug screening results was noted depending on the site of sample collection; however, a significant limitation of this case report is that none of the 3 samples were tested for fentanyl, a factor that may explain the patient's response to naloxone. Furthermore, standard urine toxicology panels do not typically detect mitragynine—the primary active alkaloid in *Mitragyna speciosa* (Kratom). Kratom, often seen as a green, powdery substance, exhibits both opioid-like and stimulant-like pharmacologic effects yet remains undetected by conventional screening methods. The patient's clinical presentation in this case report was consistent with both SC and Kratom overdose, complicating the diagnostic picture.[14] This case underscores the importance of administering naloxone in any suspected overdose given the potential for opioid involvement despite toxicological limitations.

Conclusion

As the landscape of synthetic drug use continues to evolve, clinicians must remain vigilant, adaptable, and prepared to utilize interventions, such as naloxone, regardless of the suspected causative agent or etiology of respiratory depression. Naloxone administration should remain the standard of care for suspected overdose. Its safety profile, rapid onset, and proven efficacy in opioid toxicity make it an essential tool in managing undifferentiated presentations of altered mental status and respiratory compromise. As illustrated here, naloxone may also have unexpected therapeutic benefits in cases involving SC exposure, further supporting its routine use in such scenarios.

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