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TOXICOLOGY LETTER

COMPRISING THE NEW YORK CITY AND UPSTATE NEW YORK POISON CENTERS

CASE STUDIES IN TOXICOLOGY

Series Editor: Lewis S. Nelson, MD

Synthetic Cannabinoids: The Newest, Almost Illicit Drug of Abuse

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Synthetic cannabinoids are associated with effects similar to those of cannabis. In the United States, they are growing in popularity in tandem with legal efforts to prevent their sale. In this case, a patient presents with seizures after consuming a large quantity of a synthetic cannabinoid powder that he bought online.

Case

A healthy 48-year-old man has a generalized convulsion after ingesting a powder he purchased through the Internet. The powder was sold as "research grade JWH-018," with the wording "not for human consumption" listed on the packaging. The seizures continue in the prehospital setting, as well as in the ED, for approximately 15 minutes in total before ceasing after administration of lorazepam 4 mg IV. Initial vital signs after cessation of his seizures include a blood pressure of 140/88 mm Hg; pulse, 106 beats/min; respiratory rate, 22 breaths/min; temperature, 37.7˚C. Physical examination is notable for mydriasis and diaphoresis with 5 beats of myoclonus in the bilateral lower extremities. Shortly after arrival in the ED, the patient is intubated for airway control. Findings on noncontrast CT of the brain are unremarkable, and EEG results are normal. Initial pertinent laboratory values include normal electrolyte, creatinine, and glucose levels. His creatine phosphokinase level is elevated, at 2,500 U/L. Toxicology screening does not detect acetaminophen, ethanol, or salicylates.

What is JWH-018?

JWH-018 is a synthetic cannabinoid *(Figure 1)* that acts at both endogenous cannabinoid receptor subtypes (CB1 and CB2).[1] Synthetic cannabinoids were created shortly after the structure of Δ^9-tetrahydrocannabinol (Δ^9-THC; *Figure 2*) was elucidated in the 1960s, and their development continued for use of these substances in appetite stimulants (eg, dronabinol) and as research tools for the study of the endocannabinoid receptors. Different synthetic cannabinoids have distinct binding affinity for the cannabinoid receptors. For example, HU210 is reported to bind to the CB1 and CB2 receptors with 100 times the affinity of Δ^9-THC.[2] The synthetic cannabinoids of the

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Program Announcements

UNY: The 2011 Toxicology Teaching Day is Scheduled for 11/2/11. Please mark your calendars!!

NYC: Consultants Case Conference • The first Thursday of the Month from 2-4pm

Please call administrative telephone numbers for more information and to attend remotely.

Toxicology Advice Centers

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A Toxic Swimming Pool Hazard

Rachel Weiselberg, M.D. and Lewis S. Nelson, M.D.

Case Summary:

A previously healthy 3 year-old boy is seen in a garage, playing with a cup of water over a sealed container of pool chlorinating tablets. The tablets contain TST (trichloro-s-triazinetrione; a.k.a. trichloroisocyanuric acid (TCCA) and tri-chlor). He appears outside moments later, coughing and with mild dyspnea. His mother notes a strong chlorine odor emanating from the garage. She takes him inside and gives him milk to drink. He vomits shortly thereafter. His respiratory symptoms progress and he becomes lethargic. He arrives in the ED 3 hours post-exposure.

The child presents in obvious respiratory distress. His vital signs include: BP, 91/51 mmHg; HR, 92/min; RR, 42/min; SpO2, 93% on RA; afebrile. He is lethargic, but opens his eyes to voice. His conjunctivae are erythematous. Diffuse wheezing and retractions are noted on the pulmonary exam. Skin color is normal with mildly increased turgor. Treatment is initiated with inhalational albuterol and ipratropium, intravenous methylprednisolone and magnesium sulfate, and subcutaneous epinephrine. The patient is intubated for impending respiratory failure. Chest radiograph reveals an infiltrate in the right lung field.

In the PICU the following vital signs are noted: BP, 95/59 mmHg; HR, 149/min; SpO_2, 83% on 100% FiO_2. The ventilator is set for high frequency, low volume oscillations. Repeat chest radiograph reveals diffuse bilateral infiltrates. *(Figure 1)* Laboratory data are significant for a white blood cell count of $21x10^3/mm^3$; an arterial blood gas is pH 7.20, pCO_2 45 mmHg, pO_2 60 mmHg on 100% FiO_2. Overnight, his oxygen saturation continues to fall and extracorporeal membrane oxygenation (ECMO) is initiated. *(Figure 2 shows a post-ECMO radiograph)*

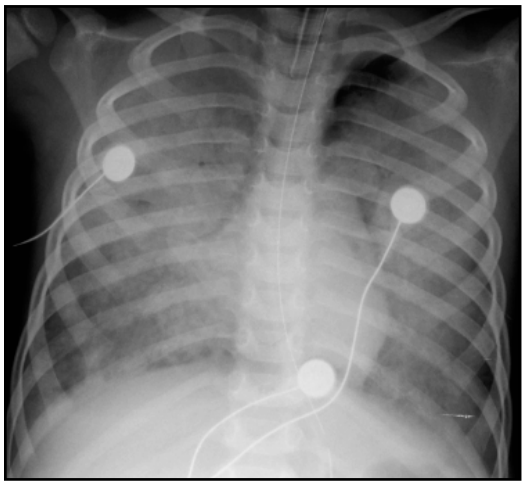

Figure 1: Initial Chest X-Ray in PICU showing diffuse bilateral infiltrates

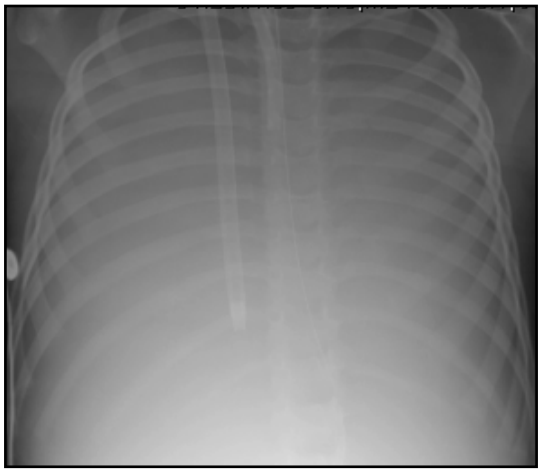

Figure 2: Chest X-Ray after initiation of extracorporeal membrane oxygenation

How does exposure occur to chlorine gas?

Chlorine, Cl_2, is a greenish-yellow gas with a characteristic odor, which is widely used for its antiseptic properties. Chlorine gas is in common use in industrial settings (such as plastic manufacture and food processing) and it finds more publicly accessible use in water treatment systems, such as community swimming pools. It can be found in pressurized cylinders for transport and delivery, or in larger sealed containers for on-site use.

For non-industrial use, chlorine is typically generated from a precursor chemical, such as TST or a hypochlorite salt. *(Table 1)* Wetting of a precursor liberates chlorine gas, which dissolves in water to generate hypochlorous acid (HOCl) and other products such as reactive oxygen species. If sufficient gas is rapidly liberated, it may escape immediate dissolution and result in ambient exposure to a nearby person. Pool chemical exposures are responsible for thousands of hospital visits each year.[1]

What are the signs and symptoms of chlorine gas inhalation?

The specific adverse clinical effects of chlorine exposure are related to the concentration (ppm) of chlorine gas and the length of time exposed. Following acute high concentration exposure, irritation of the eyes, nose and throat, may occur within minutes. With increasing duration of exposure, patients can develop chest tightness, dyspnea, cough, laryngitis, and wheezing. Acute, lower concentration exposures typically result in a delay to the onset of effects, even as late as 24 hours. In this setting, upper respiratory effects may begin nearly simultaneously with pulmonary effects. Patients may experience vomiting from upper airway irritation, and altered mental status from hypoxia. Severely affected patients may develop acute lung injury (chemical pneumonitis)

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A Toxic Swimming Pool Hazard

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Table 1: Commonly available pool chlorinating products

Chemical name	Chemical Formula	Common name	Form	Chlorine by weight	pH
Trichloro-striazinetrion	Cl3C3N3O3	Tri-Chlor	Tablet	90%	3
Dichloro-striazinetrion	Cl2C3N3O3	Di-Chlor	Granules	62%	7
Lithium Hypochlorite	Li(OCl)		Granules	35%	11
Sodium Hypochlorite	Na(OCl)		Liquid	12%	11
Calcium Hypochlorite	Ca(OCl)2	Cal-hypo	Tablet or granules	65%	12

that can progress to acute respiratory distress syndrome (ARDS). Although death following acute inhalational exposures is rare, one report of a train derailment that spilled tons of liquid chlorine in a small town produced mortality of about 1%.[2] Chronic low concentration exposures, which are often occupation related, can result in reactive airways disease, which may improve when exposure is terminated. Since chlorine gas has a higher density than air (which is primarily nitrogen) small children, due to their shorter stature, may suffer greater exposure than adults.

The toxic effects of chlorine on the pulmonary system are related to both acid formation, as explained above, and oxidative stress. In the latter situation, cytotoxic free radicals are produced. This injury generates inflammatory mediators, which activate an inflammatory response, further increasing pulmonary damage.

What therapeutic options are available to treat pulmonary injury due to chlorine gas inhalation?

Care is primarily supportive and begins with supplemental oxygen. The goal is to maintain oxygen saturation above 90%. Nebulized ß2 adrenergic agonists are provided for symptomatic patients. The use of nebulized dilute sodium bicarbonate solution (2.1-4.2%; typical clinically available sodium bicarbonate solutions are 8.4%), may neutralize the newly formed HCl and reduce pulmonary injury.[3]

Although there are case reports of oral or intravenous corticosteroid administration,[4] and animal studies suggesting a beneficial effect of corticosteroid use,[5] no controlled human studies exist. Aggravation of pulmonary superinfection in some of these patients may be a risk of use.

Endotracheal intubation should be performed as clinically indicated and conventional ventilator management may be sufficient. For patients with ARDS, high frequency ventilation (HFV), a technique that provides very rapid breaths (i.e., up to 900 breaths per minute) at very low tidal volumes may be helpful. The result is continuous positive pressure maintaining the alveoli open, while minimizing further injury to the airway. HFV appears to improve overall oxygenation and mortality in patients with ARDS.[6]

In cases where gas exchange is severely disrupted, even advanced ventilation strategies may not be adequate to oxygenate the blood. When efforts to improve oxygen delivery come at the cost of increasing lung injury, ECMO has been used successfully.[6] With ECMO, venous catheters are placed and blood is shunted through an external device that both oxygenates and removes carbon dioxide. Bypassing the lungs decreases the risk of further ventilator-induced lung trauma.

Case Conclusion:

During the second day, the patient's respiratory parameters worsened and he became increasingly hypoxic. Despite aggressive medical management, including ECMO, the parents made the difficult decision to withdraw care.

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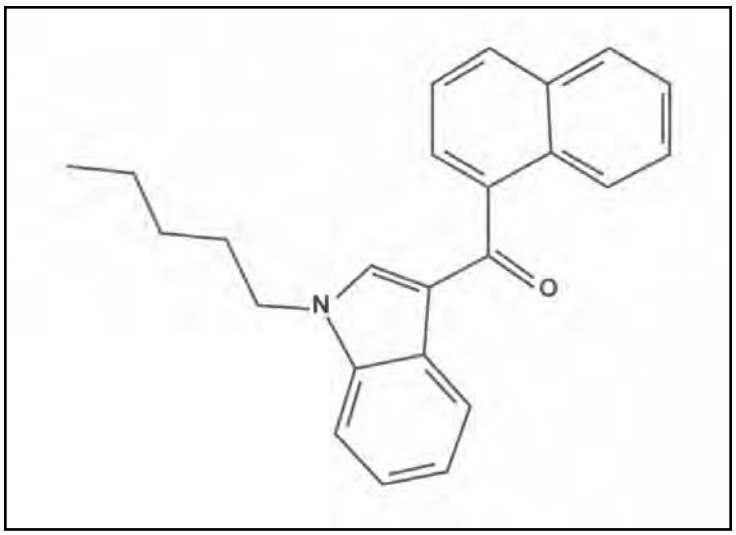

Figure 1: JWH-018

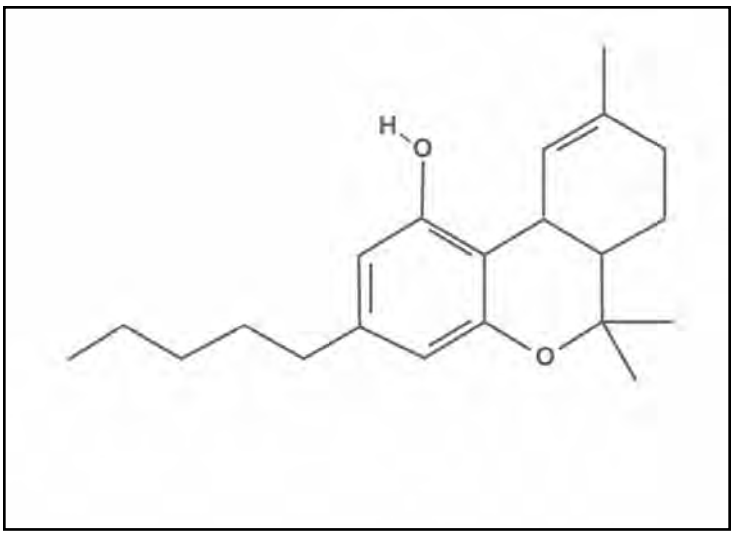

Figure 2: Δ⁹-Tetrahydrocannabinol

JWH series vary in structure from Δ⁹-THC and are classified as aminoalkylindoles. They are named for the chemist who first synthesized them, John W. Huffman, PhD (thus the "JWH" prefix). Synthetic cannabinoids recently appeared as herbal incense for sale in smoke shops and other outlets (such as gas stations). These herbal incense products contain pulverized plant material that is adulterated with one or more synthetic cannabinoids. They have been sold under multiple names and brands, including Spice, K2 *(Figure 3)*, K3, and Mr. Nice Guy. In a recently published case, JWH-018 and JWH-073 were found in a single product.[3] They are typically labeled as "not for human consumption." Purified JWH-018 is an offwhite powder that was previously used for cannabinoid receptor research.

JWH-018–laced incense first appeared in 2007 on the European drug scene. Its use peaked after a German news report detailed "legal marijuana-like" products for sale in local smoke shops.[4] Use in the United States has expanded over the last year, due largely to discussions in Internet forums.

What are the expected clinical effects of synthetic cannabinoids? How do synthetic cannabinoids differ from traditional cannabinoids?

The drug can be smoked, insufflated, or ingested. Some users report an experience similar to that of marijuana use, while others detail a more intense high that lasts longer. Not surprisingly, online user reports indicate that finding the correct recreational dose can be difficult. Although discussion in the medical literature is limited, the majority of anecdotal accounts relay clinical effects similar to those of Δ⁹-THC. The psychoactive effects (both desired and undesired) that are described include alteration of time perception, anxiety, dysphoria, listlessness, hallucinations, and psychomotor agitation. Additional undesirable effects include nausea, vomiting, tachycardia, palpitations, and xerostomia. Seizures have not been reported in users of conventional doses of JWH-018. However, given the large volume of pure JWH-018 that this patient reportedly consumed, a dose-dependent effect is likely.

What treatment can be recommended for synthetic cannabinoid–intoxicated patients?

As with marijuana users, the majority of these patients do not require measures beyond observation along with symptomatic or supportive care. Benzodiazepines are recommended for control of psychomotor agitation and abatement of seizures. Gastrointestinal decontamination has no known role in patients using synthetic cannabinoids by insufflation or inhalation. However, as with many other poisonings, it may prove beneficial in large-quantity ingestions.

What is the legal status of synthetic cannabinoids?

In November 2010, three synthetic cannabinoids (JWH-018, JWH-073, and JWH-200) were designated by the Drug Enforcement Administration (DEA) to temporary Schedule I status (i.e., they have no medicinal

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Courtesy of Cindy Moran

Figure 3: Synthetic cannabinoid products

use and high abuse potential).[5] This temporary designation applies for 1 year and could be made permanent by legislative means. The authority for temporary schedule status was enacted by the Controlled Substances Act, specifically the Analogue Act, which essentially allows structurally similar drugs with abuse potential to be removed from sale pending investigation or legal action.[6] Since these synthetic cannabinoids are not analogues of Δ^9-THC, they are not under the auspices of the Analogue Act. Furthermore, the wording of the Analogue Act states that it applies to substances "intended for human consumption" and it may well be the intention of synthetic cannabinoid manufacturers to circumnavigate this law by labeling their products as "not for human consumption." However, at this time, a temporary court injunction has halted the DEA's emergency scheduling pending further proceedings. Many of the synthetic cannabinoids are banned in Europe as well as parts of Asia.

Drs. Weiselberg and Lapoint are fellows in medical toxicology in the department of emergency medicine at the New York University School of Medicine in New York City and the New York City Poison Control Center. Dr. Nelson is an associate professor in the department of emergency medicine and director of the medical toxicology fellowship program at the New York University School of Medicine and the New York City Poison Control Center. He is also a member of the EMERGENCY MEDICINE editorial board.

Case Conclusion

The patient was extubated on hospital day 5 and had an uneventful recovery. He was subsequently discharged home in his usual state of good health.

Samples from the patient, as well as the powder he ingested, were sent for further analysis by high-performance liquid chromatography (HPLC) and gas chromatography mass spectrometry (GC/MS). The powder was found to be pure JWH-018 in crystalline form. Both JWH-018 and JWH-073 were identified in the patient's urine with unclear implications—possibly representing either the 073 compound as a metabolite of 018 or prior use of synthetic cannabinoids. Toxicologic analysis of his urine by both enzyme-multiplied immunoassay technique and GC/MS was negative for conventional drugs of abuse, including Δ^9-THC. EM

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Contributed by: Ryan Thompson MSIV

Question: What are "Bath Salts"?

Answer:

"Bath Salts" are a group of amphetamine-like compounds sold legally on the internet and in head shops. They are marketed as "bath salts" to exploit a legal loophole of the Federal Analog Act in which it is still legal to buy, sell, and possess cathinone derivatives as long as they are "not for human consumption." They are rapidly gaining popularity as drugs of abuse. They can be insufflated, ingested, or injected, although insufflation is the most popular route.

While there is consider variability between the many bath salt brands, the most commonly found compounds are methylenedioxypyrovalerone (MDPV), 4-Methylmethcathinone (mephedrone) and 3,4-methylenedioxymethcathinone (methylone). All three are cathinone derivatives, and have structural similarities to both amphetamines and MDMA. Their pharmacology is similar as well: increased neuronal release of norepinephrine, dopamine, and seratonin.

All 3 of these compounds have amphetamine-like sympathomimetic effects, such as euphoria, elevated mood, hallucinations, tremors, tachycardia, arrhythmias, hypertension, mydriasis, diaphoresis, and seizures. Methylone and mephedrone also have MDMA-like entactogenic effects, although it is unclear at this time if they have an SIADH effect like MDMA. User reports indicate potent hallucinations, agitation, and paranoia are common with these substances.

There is currently no diagnostic test for any of these compounds, as they do not appear to cross-react on standard drug screens. Diagnosis is purely based upon the history of using "bath salts." Electrolytes and renal function should be measured, with particular care to be taken to rule out an SIADH syndrome and rhabdomyolysis. Treatment is mostly supportive, using benzodiazepines as necessary for symptoms.

As the media picks up on the "bath salts" story, there has been increasing pressure on government to outlaw these substances. MDPV has already been banned in Florida and Louisiana, and several other states are in the process of banning it as well. In early February, 2011, Chuck Schumer released a statement calling for a national ban of MDPV. In the meantime, however, it appears that these drugs will continue to gain in popularity and their users will increasingly appear in our Emergency Departments.

Plant Foraging and Potential Poisonous Consequences

It is Spring in New York. Perhaps some of you have read in your local newspaper in the past few weeks articles regarding foraging. In case you have missed them, below are a couple of links for your review.

Also, within the past 2 weeks, the following case required poison center consultation;

> A 41 year old female out foraging presents to the emergency department several hours after ingesting a natural substance with multiple episodes of vomiting. Upon presentation, the patient's vital signs were also significant for a heart rate of 30 beats per minute and blood pressure of 70-80 mmHg. After intensive supportive care including the use of vasopressors, the patient had a full recovery. The plant material was identified as veratrum, a sodium channel opener affecting the cardiac cycle.

This case may seem an unlikely occurrence; however, look closely at the pictures of commonly foraged materials along side more toxic counterparts. (Lilly of the Valley is toxic, Ramps are not) As you can see from the images, mistaking plant material can be a common and unfortunate occurrence.

Newlinks:

- *http://blog.syracuse.com/cny/2011/05/where_the_wild_foods_are_stalking_edible_plants_in_the_woods_around_syracuse.html*
- *http://www.nytimes.com/2011/04/20/dining/20forage.html?_r=1&scp=3&sq=ramp&st=cse*
- *http://cityroom.blogs.nytimes.com/2011/05/14/urban-forager-ramp-season/?scp=1&sq=ramp&st=cse*

Ramps

Lily of the Valley

UPSTATE
MEDICAL UNIVERSITY
Upstate NY Poison Center
750 East Adams Street
Syracuse, NY 13210