Case Report

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Journal of Drug Abuse
ISSN 2471-853X

2018
Vol.4 No.1:4

DOI: 10.21767/2471-853X.100071

"Flakka" Intoxication: What have We Learned?

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Received date: December 19, 2017; **Accepted date:** January 07, 2018; **Published date:** January 14, 2018

Citation: Castellanos D, Menendez B, Logan BK, Mohr ALA, Ayer D, et al. (2018) "Flakka" Intoxication: What have We Learned? J Drug Abuse Vol.4 No.1:4

Abstract

Between 2014 and 2015 an outbreak of bizarre behavior and cases of excited delirium in South Florida reported in local, national and international media accounts, brought attention to the use of flakka. During that period more than 60 deaths from flakka intoxication were reported throughout the region. Treatment and intervention of potentially flakka intoxicated patients was complicated by the infrequent testing in health centers to confirm the drug's identity as reported by users or concerned others, and the challenges of determining the toxicology of the drug itself. The study described in this article reports on suspected "flakka" intoxications of patients treated at Broward Health Medical Center's Emergency Department, in Ft Lauderdale, to correlate the clinical presentation and toxicological analysis of the substances used in "flakka". The subjects' oral fluid samples were extensively analyzed by liquid chromatography, and time of flight mass spectrometry for therapeutic, recreational and novel psychoactive drugs. All six subjects recruited were male with a median age of 37; all admitted to a past history of substance use. The presence of alpha-PVP was discovered in only one subject. All subjects tested positive for multiple other drugs. Samples from five of the six subjects contained a stimulant. Nicotine/cotinine and antipsychotic medications were present in four and antihistamines were discovered in three of the samples. The routine urine drug screen was negative for half the subjects. Our knowledge of the clinical features of confirmed "flakka" intoxication is limited. Clinicians should be aware that individuals who believe they are ingesting novel psychoactive substances such as "flakka" are unknowingly using other psychoactive substances.

Keywords: "Flakka"; Alpha-PVP; Intoxication; Toxicological testing; Novel psychoactive substance

Introduction

"Flakka", believed to derive from the Spanish slang "la flaca", meaning skinny girl, is the street name given to the synthetic cathinone alpha-pyrrolidinophenone (alpha-PVP), a novel psychoactive substance (NPS) that appeared on the recreational drug market as early as 2010 [1]. The first generation of substituted cathinones was frequently referred to as "bath salts" because they were often packaged and sold as such in an effort to avoid prosecution. Early "bath salts" products contained compounds like mephedrone and methylenedioxypyrovalerone (MDVP) [2]. The drug was commonly distributed as tablets, capsules, or powders. Users reported various routes of administration, including oral, sublingual, nasal insufflation, and vaporization [3].

An outbreak of bizarre behavior and cases of excited delirium in South Florida reported in local, national and international media accounts, brought attention to the use of flakka [4,5]. As it happened with synthetic cannabinoids and synthetic cathinones in 2010-2015 [6-8]. Broward County was at the forefront of that "flakka" outbreak in South Florida between 2011 and 2015, and was possibly among the first locations in the United States to see widespread use of the drug. The use of alpha-PVP intensified in Broward County in 2014 and dramatically increased in 2015 [9,10]. Throughout Broward Health's network of hospitals 1,872 emergency department visits reported to have involved flakka from July-December 2015. In addition, in the first four months of 2015 Broward County crime lab cases had more than 400 cases involving alpha-PVP, more than any other county in the nation and more than double the total for all of 2014 (n=190) and an increase from zero reported cases in 2013 [8]. From September 2014 through December 2015 the Broward County Medical Examiner's Office reported over 60 deaths related to the use of alpha-PVP. Notably, the majority of the deaths that included alpha-PVP also involved multiple other substances [11].

During that period and to present, individuals suspected of being under the influence of the drug in a hospital setting have been infrequently tested to confirm the drug's identity as reported by users or concerned others. In addition, although "flakka's" main chemical ingredient is believed to be alpha-PVP, as with all street drugs, there is little consistency as to its actual active content. Similarly, little research exists concerning the pharmacological and toxicological effects of alpha-PVP.

These knowledge gaps about the toxicological nature of "flakka" complicate the ability of the communities affected by its use – from first responders, to medical facility professionals, to government officials – to test, treat and prevent additional deaths caused by the drug. Furthermore, the emerging use of oral fluid to determine patterns of drug use offers hope for specific, clinically relevant toxicological assays to be developed in the clinical care of acutely intoxicated persons [12,13]. Developing toxicology detection testing at the point of care that includes rapid, clinically useful identification of the active compound of a novel psychoactive drug may help practitioners to tailor their interventions to best address the needs of patients' suspected to be intoxicated with flakka or other NPS. Unfortunately such point of care toxicological detection methods do not exist and the clinical presentation of NPS, including flakka, have not yet been characterized, with the exception of case reports [14]. As a first step to address these challenges, the Department of Psychiatry & Behavioral Health at Florida International University and the Emergency Department at Broward Health Medical Center (BHMC) initiated a study aimed at examining the toxicological and clinical characteristics of flakka intoxication through a combination of toxicological testing of a collected oral fluid sample and chart review, during the height of flakka use in Broward County. Broward Health Medical Center, located in Fort Lauderdale, is the largest hospital within Broward Health, one of the 10 largest health systems in the US which managed 293,623 emergency department visits in 2015 [15].

Methods

Participant recruitment

Approved by the Broward Health System and Florida International University Institutional Review Boards, the study took place between January and April 2016. Recruited participants had to be over the age of 18 years of any gender and ethnicity, English speaking, and present to the Emergency Department (ED) at BHMC in Fort Lauderdale allegedly intoxicated with "flakka". Subjects had to be admitted to the ED based on self, family member or rapid responders' report (e.g. Broward Sherriff's Office Department, Fire Rescue). Subjects were not eligible to participate in the study if they were not able to provide informed consent, had previously participated in the study or were non-English speaking. As a safeguard and to avoid any potential issue with subjects' capacity to consent participation in the research, the investigators assessed them using a structured questionnaire - the Capacity Assessment Checklist for Research Informed Consent form (University of Alabama Human Research Protections Program, Decision-Making Capacity Assessment Tool). Based on responses, the study investigators proceeded with obtaining informed consent and completion of the consent form.

The subjects were identified for the study by two of the investigators (BM and DA), who reviewed the ED's daily census. Potential subjects identified in the ED who were too intoxicated and/or too sedated to provide consent were approached later during their stay by study staff, once their symptoms had resolved, and invited to participate.

Sample collection and analysis

Once the subjects had consented to participate, collection of oral fluid was performed. The Quantisal® collection device (Immunalysis, Pomona CA) was used to collect oral fluid for toxicological testing by trained study personnel. Oral fluid sampling has been successfully used in testing for drug use in other emergency room populations [16]. The sorbent pad was inserted into the subject's mouth and removed when the adequacy indicator turned blue (typically within 2-5 min, indicating that approximately 1 mL of sample was collected). The sorbent pad was then placed into a tube with stabilizing buffer (3 mL) for transport to the laboratory. Samples were labeled with a unique identifier to protect the subject's identity.

Upon receipt of the samples at the Center for Forensic Science Research and Education (CFSRE) in Willow Grove PA, each was analyzed using a Waters ACQUITY UPLC® I Class Waters Xevo® G2-S QTOF (LC-QTOF). The latter is a technique that allows for broad-based drug screening for over 1150 routinely encountered therapeutic and recreational drugs, including a broad range of NPS including alpha-PVP, and many other cathinone derived drugs. The database is continuously updated with additional NPS including novel stimulants, opioids, hallucinogens and synthetic cannabinoids as they appear in the recreational drug using market. Analytical separation was accomplished using an ACQUITY UPLC® BEH C18 (2.1 mm × 150 mm, 1.8 um) column at 50°C with a flow rate of 0.4 mL per minute and 5 µL injection. The Xevo® G2-S QTOF operated in positive electrospray ionization resolution mode (50-1000 m/z) with collision energy of 10-40 eV. The method's performance was based on a validated method provided by the instrument manufacturer and its performance was verified based on the qualitative validation guidelines as recommended by Scientific Working Group for Forensic Toxicology [17] as described elsewhere [18]. Following analysis, the CFSRE de-identified and disposed of the specimens.

The study investigators reviewed the medical records to collect information about the demographic and past personal history of the patients, and their physical, cognitive and psychomotor signs and symptoms as documented in the electronic health record. Demographic information included age, gender, ethnic origin, race and marital status. Past personal history included legal history, current and past substance use history and history of mental health treatment. Information regarding physical symptoms included cardiovascular, gastrointestinal, respiratory, neurologic, metabolic, ophthalmologic, renal and other physical signs and symptoms.

Psychoactive symptoms related to cognitive changes, affect, speech, behavior, psychosis and suicidal behaviors.

Routine urine drug screens and other laboratory results obtained during the hospital admission were also collected. The urine drug screen tested for benzodiazepines, cocaine, amphetamines, cannabis, opiates and barbiturates.

Table 1 Toxicological, demographic and clinical characteristics of reported flakka intoxication.

Demographics		Subject	1	2	3	4	5	6
		Age	59	28	39	46	31	35
		Sex	M	M	M	M	M	M
		Ethnicity	African American	Hispanic	African American	African American	Caucasian	Caucasian
		Legal Hx	Unknown	Unknown	Unknown	Unknown	Unknown	In jail multiple times
Behavioral Health History		Current substance use (most recent use within 1 month)	Alcohol, tobacco, cocaine, flakka	Alcohol, benzodiazepines, cannabis, stimulants unspecified flakka	Cocaine, flakka	Drugs unspecified, flakka	Alcohol, stimulants unspecified, drugs unspecified, flakka	Alcohol, drugs unspecified
		Past substance use (most recent use prior to 1 month ago)	Alcohol, tobacco	Drugs unspecified	Drugs unspecified	Drugs unspecified	Alcohol, drugs unspecified	Alcohol, drugs unspecified
		Hx of behavioral health treatment	Unknown	Substance use treatment unspecified	Prior inpatient psychiatric admission	Unknown	Mental health treatment unspecified	Mental health treatment unspecified
Current Admission	**Physical Symptoms**	Cardiovascular	None	Chest pain	Tachycardia	None	Borderline BP	None
	Psychoactive Symptoms	Gastrointestinal	None	None	None	None	None	None
		Respiratory	Productive cough	None	None	None	None	None
		Neurological	Headache, blurred vision	None	None	None	None	None
		Metabolic	None	None	None	None	None	None
		Ophthalmologic	None	None	None	None	None	None
		Renal	None	None	None	None	None	None
		Muscular	Chest tenderness to palpation	Elevated CPK1	Elevated CPK1	Elevated CPK1	Elevated CPK1, Rhabdomyolysis	Elevated CPK1
		Other Physical Sxs	Left side chest pain radiating to Left arm and Left leg	None	None	None	None	None
	Psychoactive Symptoms Laboratory	Cognitive	Alert, Oriented x 3	Altered mental status	Alert, Oriented x 3	Altered mental status	Alert, Oriented x 3	Alert, Oriented x 3
		Affective	Appropriate	Hostile	Anxious	Anxious	Suicidal	Hostile
		Speech	Clear	None	None	None	None	Hostile

		Behavioral	Uncooperative	Belligerent	Agitated	Agitated	Belligerent	None
		Psychosis	None	None	None	Paranoia	None	Belligerent
		Suicidality	None	None	None	None	Ideations	None
	Medications Administered Prior to Study Sample Collection		Aspirin	Lorazepam	None	None	Lorazepam	Lorazepam
			Morphine	Olanzapine			Olanzapine	Olanzapine
			Nitroglycerine	Diphenhydramine			Diphenhydramine	Diphenhydramine
			Lorazepam					
			Acetaminophen					
			Enoxaparin					
	Laboratory	Urine Drug Screen	Negative	Cannabis, Benzodiazepines	Negative	Negative	Ethanol	Cannabis, Ethanol
		Time from arrival at ED to oral sample collection	1,010 min	621 min	374 min	299 min	1,045 min	912 min
		Oral Fluid Toxicology Results	Alpha-PVP Benzoylecgonine	Cocaine	Cocaethylene	Benzoylecgonine Cocaethylene	Caffeine	Caffeine
			Cocaine	Diphenhydramine	Cocaine	Cocaine	3,4-Methylenedioxyamphetamine	Chlordiazepoxide
			Cotinine	Olanzapine	Norcocaine	Cotinine	Olanzapine	Chlorpheniramine
			Ecgonine Methyl Ester Levamisole		Cotinine	Diphenhydramine	Yohimbine	Cotinine
			Methamphetamine		Ecgonine Methyl Ester Levamisole/ tetramisole Nicotine	Ecgonine Methyl Ester Haloperidol		Haloperidol
						Hydroxycocaine		Olanzapine
						Hydroxyzine Levamisole/ tetramisole Nicotine		
						Norcocaine		

Results

Our convenience sample was comprised of six subjects recruited for the study who reported they had ingested flakka prior to admission and presented as intoxicated to the ED. Five other potential participants met the enrollment criteria, but declined to participate or were discharged before being approached regarding their participation.

Subjects' ages ranged from 28-59 with a median age of 37 years. All six subjects were male; three were African American, two Hispanic and one Caucasian. All six subjects admitted to a past history of substance use, with five subjects (83%) acknowledging cocaine or stimulant use, and four (67%) admitting to "flakka" and to alcohol use within 30 days of their admission to the hospital. Only one subject reported a history of substance abuse treatment, although half of the group had received prior mental health treatment.

The toxicological testing of the oral fluid samples found the presence of alpha-PVP in only one subject. However, all subjects believed they had ingested "flakka". That finding is limited by the as of yet unknown half-life of alpha-PVP in humans compared to studies in non-humans [19,20]. Related pyrovalerones such as methylenedioxypyrovalerone (MDPV) are documented to yield periods of acute intoxication of 6-8 h [21].

Although at the time of the ED visit each of the subjects was reportedly under the influence of the drug our team of researchers was not able to ascertain the specific time of ingestion of the drug prior to admission. Therefore we used the

time of admission to the hospital as a proxy to understand the time interval between ingestion and sample collection. The mean time from arrival in the ED to sample collection was 707 min.

Each subject tested positive for multiple drugs. Five of the six oral fluid samples contained a stimulant (alpha-PVP, cocaine, methamphetamine, 3,4-Methylenedioxeamphetamine). Nicotine/cotinine and antipsychotic medications were present in four of the samples and antihistamines in three of the samples. Olanzapine was administered in the hospital prior to the oral fluid sample collection and appropriately detected in the oral fluid of each of the three subjects. Haloperidol was not administered to any subjects but detected in two samples. The routine hospital urine drug screen was positive for cannabis use in two subjects and alcohol for two but negative for 50% of the subjects **(Table 1).**

Physical symptoms observed during each subject's intoxication were variable. Minimally relevant gastrointestinal, respiratory, neurological and renal symptoms were observed. Although the toxicological results suggest all but one of the subjects had ingested a potent CNS stimulant, prominent cardiovascular symptoms (such as, tachycardia) were not observed. Five out of the six subjects showed increased creatine phosphokinase (CPK) levels during their hospital stays. The main psychoactive symptoms reported by hospital staff included belligerent or agitated behavior (6/6 subjects) and hostility and anxiety, observed in five of the six subjects. One subject presented with paranoid thinking and one with suicidal ideation. The subject whose toxicological testing confirmed ingestion of alpha-PVP was the only subject who displayed chest pain/ tenderness with irradiation down the left arm, a productive cough, headache and blurry vision **(Table 1).**

Discussion and Conclusion

The results support the experience of observers, users, and clinicians to have highlighted that people who believe they are ingesting drugs such as "flakka" are unknowingly using other psychoactive substances [22-24]. Our study, however, is the first to describe and confirm the toxicological and clinical characteristics of individuals reported to have presented with "flakka" intoxication in an acute care setting.

Our finding that the routine urine drug screen was negative for half of the subjects is consistent with previous literature demonstrating the limitations of many routine urine drug screen panels in identifying novel psychoactive drugs [25,26]. Our study lends further support to the fact that these emerging NPS present many challenges. Users never truly know what they are ingesting; clinicians, in the absence of confirmatory toxicological testing, are equally uncertain.

Publications supposedly describing the clinical symptoms of NPSs continue to emerge [27]. Our results clearly support interpreting with caution these published reports that lack toxicological or chemical confirmation of the specific drug involved (ideally in a biological sample, along with a quantitative measurement) or at least of the material ingested by the individual. Even when toxicological analysis is available, the presence of multiple substances makes it difficult to assign unique clinical effects to specific substances.

Our study was limited by the small number of subjects who presented to our ED since the latter part of 2015 and by the time the study was approved by the IRB. The study was terminated after 150 days due to no patients presenting to the ED reporting "flakka" ingestion. The decrease in persons claiming to be intoxicated with "flakka" appears to be principally the result of unprecedented coordination among local groups to fight "flakka's" demand and possibly more importantly, the willingness of the Chinese government to ban alpha-PVP and 115 other novel psychoactive substances on October 1, 2015 [11,28]. In addition, the specific time of ingestion of the drug prior to admission was unknown. Approximately 12 h elapsed from the arrival to the ED until sample collection. Consequently, if "flakka's" half-life is similar to MDPV when taken by the patients it is possible that the chemical agent responsible for the subject's intoxication was metabolized below detectable limits by the time the sample was collected.

In spite of the limited sample studied it is hoped that other clinicians and researchers can build on the findings and learn from them. Alpha-PVP and other synthetic cathinones remain a challenging group of novel psychoactive drugs that present potentially dangerous health effects and that must be contained and documented toxicologically. These compounds have evolved rapidly since first appearing on the world market a few years ago. Identifying specifically which compound an individual has ingested can be difficult. The clinical effects and safety profile of these drugs is largely unknown. Emergency department clinicians are, therefore, left in a difficult situation. The history that is available with acutely intoxicated patients is minimal and often unreliable. As we have demonstrated even if the history suggests or the patient reports having ingested a certain drug, the chemical and toxicological composition is typically unknown and frequently not consistent with the substance reportedly ingested. The diagnosis remains primarily clinical with toxicological confirmation difficult due to expense, turnaround times and manufacturers constantly developing new analogues to avoid detection. Clinicians in acute care settings typically treat clinical symptoms without truly knowing what drug is producing the clinical presentation. An urgent need exists for clinicians to be familiar with the effects of these ever-changing psychoactive compounds. Future efforts should continue to develop rapid and agile strategies, as well as confirmatory and descriptive studies like the one presented here, to recognize and report these new drugs as they emerge [29,30].

Acknowledgment

The authors wish to thank Priscilla Chaves, Carolina Cardenas and Aniuska Luna for their assistance with the coordination of this project and Melissa Friscia for performing the analysis of the specimens.

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