The delirious substance abuser

Raphael J. Leo, MD, MA, and Ritu Goel, MBBS

How would you handle this case?

Visit **CurrentPsychiatry**.com to input your answers and see how your colleagues responded

In the ER, Ms. K, age 29, is inattentive, confused, and experiencing tachycardia and acute renal failure. She has a history of cocaine and marijuana use, but could there be another cause?

CASE Hurt and confused

Emergency medical services (EMS) are called to Ms. K's apartment after her roommate found her lying on the floor moaning. The roommate tells EMS that Ms. K, age 29, appeared confused and was slurring her words, and reports that this change in her awareness progressed rapidly over a few hours. EMS personnel find that Ms. K has multiple contusions on her arms and face, which they presume to be self-inflicted. A marijuana pipe is discovered at Ms. K's apartment.

In the emergency room (ER), Ms. K is inattentive and has difficulty following simple commands. Her speech is mumbled and her thoughts are disorganized. She displays psychomotor restlessness in the form of combativeness. Ms. K cannot provide meaningful historical data and is disoriented to place and time. The ER staff requests a psychiatric consultation.

Family members reveal that Ms. K has no preexisting medical conditions, is not taking prescription medications, but has a history of substance abuse (sporadic cocaine and cannabis use). Her family is unaware of recent substance use.

Physical examination reveals tachycardia (heart rate 110 to 120 beats per minute), hypotension (blood pressure 78/49 mm Hg), hypothermia (temperature 88°F), and peripheral pulse oximetry of 84%. Her pupils are dilated and reactive to light; no conjunctival injection is noted. Her lung fields are clear on auscultation, but she is noted to have a rapid, irregular heartbeat. The abdomen is positive for bowel sounds, soft on palpation, and without any repositioning or notable overt signs of tenderness. Ms. K's toes show purple discoloration with poor capillary refill. The dorsalis pedis pulses are reported to be 1+ bilaterally; however, the remainder of the arterial pulse examination is normal.

Her sodium, potassium, and chloride values are normal, but she has an abnormal anion gap (28.1 mEq/L), blood urea nitrogen (53 mg/dL), creatinine (2.9 mg/dL), creatine kinase (10,857 U/L), creatine kinase MB (432.6 ng/mL), and hyperglycemia (glucose 425 mg/dL). Arterial blood gas reveals hypoxia (P_{O_2} of 55 mm Hg), with metabolic acidosis (sodium bicarbonate 10 with compensatory P_{CO_2} of 33 mm Hg). Her urine is cloudy, positive for protein, ketones, hemoglobin, and glucose. She is thought to have a high anion gap acidosis related to dehydration, lactic acidosis (lactic acid 20 mEq/L), and hyperglycemia. Urine toxicology is positive for cannabinoids; ethylene glycol and methanol screen negatively, which rules these out as potential contributors to her high anion gap acidosis.

Dr. Leo is Associate Professor and Dr. Goel is Assistant Clinical Instructor, Department of Psychiatry, State University of New York at Buffalo, Buffalo, NY.

Ms. K is intubated and IV fluids are initiated for rhabdomyolysis and acute renal failure. Dialysis is implemented on a short-term basis. Her mental state improves gradually over 3 days.

What is your differential diagnosis?

a) delirium due to general medical condition
b) substance-induced delirium
c) cannabis intoxication
d) cocaine intoxication
e) seizure

The authors' observations

Based on the abrupt onset of inattention and confusion, disorganized speech, memory impairments, and psychomotor agitation, we made an initial diagnosis of delirium; however, the precise etiology remained unclear. DSM-IV-TR diagnostic criteria for delirium are described in ***Table 1.*** Although delirium due to multiple etiologies does not have a DSM-IV-TR coding designation, we speculated that multiple causes contributed to Ms. K's presentation. Acute renal failure secondary to dehydration as well as rhabdomyolysis, hypoxia, and hyperglycemia were implicated as general medical conditions etiologically linked to delirium. Because Ms. K has no preexisting medical conditions and her roommate and family stated she had a history of substance abuse, we also considered a presumptive diagnosis of substance-induced delirium. The medical team speculated that, based on information provided by her family, Ms. K may have had a seizure or may have fallen, which would account for her multiple contusions, and could have led to muscle injury and breakdown and the resultant rhabdomyolysis.

The possibility of cannabinoid-induced delirium has been reported, albeit rarely.[1-3] However, Ms. K's presentation—hypothermia, variable heart rate, lack of dry mucous membranes—was not consistent with significant anticholinergic toxicity or cannabinoid intoxication (***Table 2, page 60***).

Table 1

DSM-IV-TR criteria for delirium due to multiple etiologies

A. Disturbance of consciousness (ie, reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention
B. A change in cognition (such as memory deficit, disorientation, language disturbances) or the development of a perceptual disturbance that is not better accounted for by a preexisting, established, or evolving dementia
C. The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day
D. There is evidence from the history, physical examination, or laboratory findings that the delirium has >1 etiology (eg, >1 etiological general medical condition, a general medical condition plus substance intoxication or medication side effect)

Source: Diagnostic and statistical manual of mental disorders, 4th ed, text rev. Washington, DC: American Psychiatric Association; 2000

By contrast, cocaine-induced delirium has been reported and initially appeared to be a plausible cause of Ms. K's symptoms (***Table 2, page 60***). Delirium related to excess ingestion of cocaine may be related to the drug's secondary effects resulting in rhabdomyolysis and renal dysfunction.[4-6] Although several mechanisms underlying this relationship have been proposed, no single specific mechanism has been identified. The basis for cocaine ingestion and the resultant metabolic and renal effects, as observed in Ms. K's case, likely are multifactorial. Mechanisms of the rhabdomyolysis might include:

- blockade of synaptic catecholamine reuptake and induction of adrenergic agonism, resulting in vasoconstriction and ischemia and leading to muscle damage
- cocaine-induced seizures and/or prolonged unconsciousness, leading to muscle compression and breakdown of muscle tissue

Clinical Point

Cocaine-induced delirium may be related to the drug's secondary effects resulting in rhabdomyolysis and renal dysfunction

continued

Table 2

Diagnostic criteria for cannabis and cocaine intoxication

Diagnostic criteria	Cannabis intoxication	Cocaine intoxication
Recurrent use	+	+
Symptom onset	During or shortly after use	During or shortly after use
Behavioral changes	Impaired motor coordination	Hypervigilance, stereotyped behaviors
Psychological changes	Euphoria, anxiety, sensation of slowed time, social withdrawal, impaired judgment	Euphoria, anxiety, tension, anger, changes in sociability, interpersonal sensitivity, impaired social or occupational functioning
Associated criteria (≥2)	Conjunctival injection, increased appetite, dry mouth, tachycardia	Tachycardia or bradycardia, papillary dilation, elevated or lowered blood pressure, chills/perspiration, nausea/vomiting, evidence of weight loss, psychomotor changes, muscular weakness, chest pain, cardiac arrhythmias, seizure, dyskinesia, dystonia, delirium, coma

Source: Diagnostic and statistical manual of mental disorders, 4th ed, text rev. Washington, DC: American Psychiatric Association; 2000

Clinical Point

Sold as 'bath salts,' MDPV can be acquired from Internet sources and is used as a recreational drug

- a period of exertion induced by cocaine, precipitating an excited delirium and associated rhabdomyolysis
- a surge in dopamine concentrations, similar to neuroleptic malignant syndrome, precipitates hyperthermia, muscle rigidity, and psychomotor agitation, disrupting neuromuscular homeostasis and leading to rhabdomyolysis.

We were uncertain about the plausibility that acute cocaine intoxication caused Ms. K's medical sequelae, in light of her toxicology findings. If cocaine use was the inciting event, and because the delirium reportedly had developed over several hours, we would expect cocaine to be detected in the toxicology screen. However, it was not detected. Cocaine can remain detectable in urine for 2 to 4 days,[7] which raised our speculation that remote cocaine abuse could account for Ms. K's current presentation and the timeline the roommate initially relayed to EMS personnel was inaccurate. We needed to clarify the timeline and progression of Ms. K's symptoms with the roommate. In addition, we suggested to the medical team that alternative substances of abuse could be causing Ms. K's symptoms and the roommate might be the only person who could unveil this possibility.

What other agent(s) should be considered as causes for Ms. K's delirium?

a) amphetamine
b) methylenedioxymethamphetamine (MDMA, "ecstasy")
c) methylenedioxypyrovalerone (MDPV)
d) A and B

HISTORY Unknown substance

Ms. K's roommate is contacted for supplemental history. The roommate reports that recently he observed Ms. K "snorting" a brown/tan-colored substance. He had not seen her use this substance previously, and when he asked her what it was, she reportedly said that it was "PeeVee" (also called "bath salts") purchased over the Internet.

The authors' observations

MDPV is a novel chemical compound that is used as a recreational drug (***Table 3, page 65***).[8] It commonly is acquired from Internet sources and sold as "bath salts." Its use first emerged in approximately 2004, and its popularity has been increasing because of its easy availability and relatively low cost.[9] The American Association of Poison Control Centers received 302 calls related to MDPV toxicity in 2010 and 5,625 calls

continued on page 65

continued from page 60

Table 3

Overview of MDPV features

Chemical name	3,4-methylenedioxypyrovalerone
Popular names	MDPV, PV, PeeVee, Super coke, Magic
Sources	Sold as "bath salts" by Internet sources, "head shops," and gas stations
Mode of use	Oral, snorting, smoking, rectal insertion, intravenous
Acute effects	Increased energy, perception of heightened alertness/attention, aphrodisiac properties, increased sociability
Adverse psychological effects	Anxiety (panic attacks), irritability, agitation, confusion, suicidal ideations, visual distortions
Adverse physical effects	Insomnia/overstimulation, bruxism, muscle twitching, pupil dilation/blurred vision, anorexia, headache, nausea/vomiting, hyperthermia, irregular heart beat, tachycardia, dyspnea, fatigue
Effects of protracted use	Dysphoria, depression, anhedonia
LD_{50}	Unknown

LD_{50}: lethal dose; MDPV: methylenedioxypyrovalerone

Source: Reference 8

related to MDPV use between January 1 and October 31, 2011.[10,11]

MDPV has psychoactive properties, with stimulant effects acting as a norepinephrine-dopamine reuptake inhibitor.[8,9,12] When snorted, ingested orally, or inserted rectally, the agent produces effects comparable to cocaine or psychostimulants such as methylphenidate or dextroamphetamine.

Acute effects of MDPV include heightened alertness, diminished need for sleep, hyperarousal, and euphoria.[8,9] These symptoms often are accompanied by increases in heart rate and blood pressure, sweating, and peripheral vasoconstriction. Individuals may abuse MDPV to acquire sustained attention, reduce their need for sleep, or for aphrodisiac effects. In many cases, anxiety and irritability can accompany the desired euphoric effects. For some, the euphoric effects can be superseded by anxiety or agitation. Mood and attention effects are estimated to last 3 to 4 hours; however, tachycardia and hypertension can persist for 6 to 8 hours.

MDPV use can trigger cravings and lead to binging. Euphoric stimulation with MDPV can become dysphoric as the dose and duration of use increase. Extended use has been associated with agitation, irritability, aggression, panic and marked anxiety, psychosis, and delirium.[8,9] Anxiety can range from mild dysphoric stimulation to extreme panic-like states. In moderate forms, a state of sympathetic discharge can occur, producing physiologic effects resembling panic attacks, including hypertension, tachycardia, sweating, and peripheral vasoconstriction. In more severe cases, users may experience a feeling of impending doom, marked distress, and frank psychosis. Patients may experience disorientation and unsystematized paranoid delusions. Case reports of intoxication have described self-injurious behaviors, such as cutting, which may account for the contusions observed on Ms. K's face and arms. Increasingly, MDPV use has resulted in ER presentations with patients manifesting abrupt onset confusion, anxiety, and self-injurious behaviors.

The mechanisms underlying MDPV-induced delirium have not been definitively identified. Given the similarities in mechanism of action between MDPV and cocaine, causes for delirium related to MDPV are similarly presumed to be multi-

Clinical Point

Acute effects of MDPV include heightned alertness, hyperarousal, and euphoria

Related Resources

- American Screening Corp. (MDPV screening). www.americanscreeningcorp.com.
- U.S. Drug Enforcement Administration. 3, 4-Methylenedioxypyrovalerone (MDPV). www.deadiversion.usdoj.gov/drugs_concern/mdpv.pdf.
- Prosser JM, Nelson LS. The toxicology of bath salts: a review of synthetic cathinones [published online ahead of print November 23, 2011]. J Med Toxicol. doi: 10.1007/s13181-011-0193-z.

Disclosure

The authors report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

Clinical Point

MDPV is not detected on routine toxicology screens; however, it can be identified with gas chromatography/mass spectroscopy

factorial. The course of delirium associated with MDPV intoxication is self-limited and requires supportive measures.[8,9]

Suspect MDPV abuse in patients who present with signs or symptoms of stimulant intoxication but have a negative toxicology screen for cocaine and other psychostimulants. MDPV is not detected on routine toxicology assessments; however, it can be identified through laboratories with gas chromatography/mass spectroscopy capabilities. However, the time needed to obtain the results may exceed the clinical course of the patient's delirium. One of the limitations in Ms. K's case was the lack of gas chromatography/mass spectroscopy to confirm MDPV ingestion. Ms. K's roommate could not locate any unused brown powder within their apartment to bring in for laboratory investigations. Recently, screening assessments for MDPV have become commercially available (see ***Related Resources***).

OUTCOME Referral to treatment

Dialysis is discontinued within 1 day of hospitalization. Ms. K's peripheral arterial perfusion improves, as does her thermoregulatory status. Her mental status improvements coincide with improvements in her physical and metabolic status.

Ms. K is able to sustain attention when speaking with interviewers. She is aware of her surroundings and is no longer distracted by extraneous stimuli. Her speech is articulate and her thoughts are linear. There is no evidence of any residual thought disorganization, delusions, or hallucinations.

Initially, Ms. K is reluctant to acknowledge her substance use, but eventually, she concedes to acquiring a stimulant from an Internet source and abusing it in undetermined amounts. She had no experience with using MDPV and did not know how to avoid ingesting dangerous amounts. We educate Ms. K about the dangers she faced during this hospitalization and the potential life-threat-

ening outcomes. She is amenable to pursuing outpatient substance abuse treatment. Her roommate is enlisted to facilitate her follow-up with this treatment.

The authors' observations

Managing MDPV toxicity presents a diagnostic dilemma for medical personnel and psychiatrists when evaluating and managing acute delirium. MDPV ingestion may go unrecognized in clinical settings because toxicology assessments for it are not readily available and patients' historical information may be unreliable.

Because of the seriousness of sequelae associated with MDPV use, state and federal agencies have intervened. Until recently, bath salts did not have a controlled substance designation. In October 2011, the US Drug Enforcement Administration (DEA) ruled to make MDPV a controlled substance for 1 year, with the possibility of a 6-month extension.[13] Although this ruling is temporary, it makes possession, sale, or distribution of these chemicals, or the products that contain them, illegal in the United States. In the interim, the DEA and the US Department of Health and Human Services will determine whether MDPV should remain a controlled substance.

References

1. André C, Jaber-Filho JA, Bento RM, et al. Delirium following ingestion of marijuana in chocolate cookies. CNS Spectr. 2006;11(4):262-264.
2. Hollister LE. Health aspects of cannabis. Pharmacol Rev. 1986;38(1):1-20.
3. Meyer ME. Psychiatric consequences of marijuana use: the state of the evidence. In: Tinklenberg JR, ed. Marijuana and health hazards: methodologic issues in current research. New York, NY: Academic Press; 1975:133-152.
4. Ruttenber AJ, Lawler-Heavner J, Yin M, et al. Fatal excited delirium following cocaine use: epidemiologic findings provide new evidence for mechanisms of cocaine toxicity. J Forensic Sci. 1997;42(1):25-31.
5. Ruttenber AJ, McAnally HB, Wetli CV. Cocaine-associated rhabdomyolysis and excited delirium: different stages of the same syndrome. Am J Forensic Med Pathol. 1999;20(2):120-127.
6. Singhal PC, Rubin RB, Peters A, et al. Rhabdomyolysis and acute renal failure associated with cocaine abuse. J Toxicol Clin Toxicol. 1990;28(3):321-330.
7. Moeller KE, Lee KC, Kissack JC. Urine drug screening: practical guide for clinicians. Mayo Clin Proc. 2008;83(1):66-76.
8. Psychonaut WebMapping Research Group. MDPV report. London, United Kingdom: Institute of Psychiatry, King's College. http://www.psychonautproject.eu/documents/reports/MDPV.pdf. Accessed November 23, 2011.
9. Ross EA, Watson M, Goldberger B. "Bath salts" intoxication. N Engl J Med. 2011;365(10):967-968.
10. American Association of Poison Control Centers. Bath salts data. http://www.aapcc.org/dnn/Portals/0/Bath%20Salts%20Data%20for%20Website%2011.03.2011.pdf. Updated November 3, 2011. Accessed November 23, 2011.
11. Centers for Disease Control and Prevention. Emergency department visits after use of a drug sold as "bath salts"—Michigan, November 13, 2010-March 31, 2011. MMWR Morb Mortal Wkly Rep. 2011;60(19):624-627.
12. Westphal F, Junge T, Rösner P, et al. Mass and NMR spectroscopic characterization of 3, 4-methylenedioxypyrovalerone: a designer drug with α-pyrrolidinophenone structure. Forensic Sci Int. 2009;190(1-3):1-8.
13. U.S. Drug Enforcement Administration. Chemicals used in "bath salts" now under federal control and regulation. http://www.justice.gov/dea/pubs/pressrel/pr102111.html. Accessed November 23, 2011.

Clinical Point

In October 2011, the US DEA made MDPV a controlled substance, which made its possession, sale, or distribution illegal

Bottom Line

Methylenedioxypyrovalerone (MDPV)—also known as 'bath salts'—is a possible etiology of acute delirium in patients with no preexisting medical conditions. Routine toxicology investigations cannot detect MDPV and delirium in the context of a negative toxicology screen may be the only sign of MDPV ingestion. Supportive measures are required. Referral to substance abuse treatment and psychiatric follow-up are essential in the long-term management of these patients.