Violent Behavior and Hallucination in a 32-Year-Old Patient

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CASE

A 32-year-old white male was brought to the emergency department by police after a sudden, dangerous outburst. He had allegedly assaulted his girlfriend and attempted to run her over with his car. Subsequently, the patient reportedly stole and/or damaged numerous other motor vehicles. Several security and law enforcement officers were required to subdue the patient and bring an end to his hallucination-driven rampage, which lasted about 2 hours. The patient’s medical history included chronic back pain, hypertension, and a long history of substance abuse, including alcohol, tobacco, and marijuana. A physical examination revealed the following: blood pressure, 132/88 mmHg; heart rate, 135 beats/min; respiratory rate, 18/min; body temperature, 98.7 °F; oxygen saturation, 98% on room air. He was markedly anxious, distressed, and sweating profusely. His pupils were normal in size and reactive to light. The patient had mild abrasions on his hands, arms, and shoulders, but he had no severe injuries. He progressively became more agitated in the emergency department and required 10 mg ziprasidone intramuscularly and 2 mg lorazepam intravenously for sedation. Intoxication with psychoactive substances was suspected; however, the results of routine screening tests of serum and urine samples were negative for alcohols, amphetamines, cocaine, and opioids.

DISCUSSION

For cases in which drug abuse is high on the differential but the results of routine drug screening are negative, physicians and laboratorians should consider the analytical sensitivity and specificity of the assays they have used to perform the screen. For example, although a patient may have overdosed on oxycodone, does the laboratory’s general opiate immunoassay detect this synthetic opioid? Local availability and use of illicit drugs, including designer drugs, also need consideration. Phencyclidine can induce a clinical presentation similar to the one described above, but it is rarely used in our region and is therefore not included in the routine drug screening at our hospital. Overdose with prescription medications (as in the case of oxycodone) may also give a negative screen result for drugs of abuse. It may be necessary to use more-specific analytical methods, such as mass spectrometry, to detect the latest derivatives of designer drugs, for which immunoassays are not available. Other limitations of immunoassay-based drug screening include lack of analytical specificity for individual compounds, the high cost of reagents, lot-to-lot variation, and a relatively high susceptibility to interferences.

PATIENT FOLLOW-UP

An astute resident physician had seen recent suspected cases of intoxication with “bath salts”—synthetic cathinones packaged as hygiene products, insect repellent, or plant food—and recognized in this patient the signs of intoxication reported by patients with this class of drugs (1). The resident contacted the laboratory and asked whether in-house toxicology tests would be capable of detecting synthetic cathinones in serum or urine. Roche Diagnostics, the manufacturer of the amphetamine-screening test, indicated that cross-reactivity with synthetic cathinones had not been tested.

Poison control centers in the US received 303 calls regarding drug exposures attributed to “bath salts” during 2010. Between January 1 and August 31, 2011, the number of these calls increased drastically, to 4720 (2). The psychoactive drugs being marketed as “bath

QUESTIONS TO CONSIDER

1. What drugs should be considered in cases in which drug abuse is suspected but the results of all drug screens are negative?
2. What are the limitations of immunoassay-based drug screening?
3. What would be the ideal analytical method for comprehensive drug screening?
“Bath salts” are synthetic derivatives of cathinone, the active compound found in Catha edulis, a plant endemic to East Africa and the Middle East. Scores of cathinone derivatives more potent than the herbal compound have been described. Structures for a few common synthetic cathinones are given in Fig. 1.

Synthetic cathinones are believed to be synthesized from ephedrine or pseudoephedrine by underground chemists and then packaged and marketed as bath salts, insect repellent, plant food, or stain remover. A multiplicity of colorful brand names have been used (e.g., Cloud 9, Vanilla Sky, Ivory Wave, White Lightning) on packages for sale by gas stations, head shops, adult book stores, and Internet suppliers (1, 5, 6). These drugs are taken orally, intranasally, intravenously, or rectally and have highly addictive potential. Like other sympathomimetics, synthetic cathinones appear to stimulate the central nervous system via inhibition of norepinephrine and dopamine reuptake mechanisms. Toxic or negative effects associated with synthetic cathinone abuse include intense hallucinations, hyperthermia, hypertension, tachycardia, and other extreme sympathomimetic and behavioral effects. Preparations of synthetic cathinones may be sold as mixtures or coingested with other drugs, complicating the clinical picture.

Despite structural similarities to other sympathomimetic amines (Fig. 1), routine immunoassay-based drug screens for amphetamines have not detected synthetic cathinones. Advanced detection methods based on LC-MS or GC-MS are not routinely available. Although sending samples to a reference laboratory is not useful for emergency situations or short-term hospital care, testing for synthetic cathinones may be vital to forensic investigations or for differential diagnosis of psychiatric conditions. In addition, as yet unrecognized long-lasting health effects may be connected with abuse of this class of drugs, as has been suggested for chronic abuse of amphetamines. Thus, it may be important for clinicians to have appropriate laboratory testing available to confirm the presence of one or more of the synthetic cathinones.

Regional differences in drug availability have been noted. Methcathinone and mephedrone (4-methyl-N-methylcathinone) have been the most commonly reported cathinone derivatives in Eastern and Western Europe, respectively, in the past 2 decades. Most recently, Spiller et al. found 3,4-methylenedioxypyrovalerone (MDPV) to be the predominant synthetic cathinone detected in 19 “bath salts” cases at 2 poison control centers in the central part of the US during 2010 (5). Public health officials, law enforcement officials, and legislators in several states and in Europe have acted quickly to ban members of this new class of drugs. On October 21, 2011, the US Drug Enforcement Administration issued a final order to place 3 synthetic cathinones temporarily in Schedule I: mephedrone, 3,4-methylenedioxymethylcathinone (methylone), and MDPV (9).

**CASE RESOLUTION**

The patient confessed to snorting an unknown brand or quantity of “bath salts” approximately 6 hours before...
Table 1. Linear-gradient conditions for LC-MS/MS detection of MDPV.

<table>
<thead>
<tr>
<th>Time, min</th>
<th>Flow rate, mL/min</th>
<th>Mobile phase A, %</th>
<th>Mobile phase B, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–2.20</td>
<td>0.400</td>
<td>90.0</td>
<td>10.0</td>
</tr>
<tr>
<td>2.20–2.30</td>
<td>0.400</td>
<td>20.0</td>
<td>80.0</td>
</tr>
<tr>
<td>2.30–3.00</td>
<td>0.400</td>
<td>5.0</td>
<td>95.0</td>
</tr>
</tbody>
</table>

CONCLUSION

This case study illustrates the major threat that abuse of synthetic cathinones poses to both the individual and the public, especially when hallucinations and violent behavior are manifested. Clinical laboratories should be aware of current designer drugs and be prepared to facilitate testing when appropriate. Our inquiries to 8 manufacturers of amphetamine drug screen tests revealed that only 3 of them had some data on the cross-reactivity of select synthetic cathinones. These 3 products demonstrated insufficient cross-reactivity to meet the clinical need in cases of designer drug intoxication at the concentrations previously reported (5). The geographic distribution and structural features of designer drugs change rapidly, more rapidly than immunoassays can be developed and validated.

The ideal analytical method for comprehensive drug screening would involve mass spectrometry, which is currently the only analytical approach available for detection of synthetic cathinones or other designer drugs. Analytical reference standards become available relatively quickly, owing to the close collaboration of suppliers, poison control centers, and government agencies. Thus, mass spectrometry methods can be validated rapidly for detection of the latest iterations of designer drugs. Although current mass spectrometry methods also have limitations for routine drug screening in many laboratories, namely the cost of instrumentation and increased turnaround times, they can provide up-to-date and comprehensive drug screening for emergency situations when in-house mass spectrometry methods can be made available.

POINTS TO REMEMBER

- “Bath salts,” a new form of designer drug, are synthetic cathinones packaged as hygiene products, insect repellent, or plant food. Three synthetic cathinones are now temporarily in Schedule I: mephedrone, methylene, and MDPV.
- Patients with extreme sympathomimetic syndrome, hallucinations, and violent behavior may have taken one of many possible synthetic cathinones.
- Street names for this class of drugs vary widely and may represent mixtures of drugs.
- Routine screening for drugs of abuse may not detect synthetic cathinones.
- Testing for synthetic cathinones should be facilitated with close communication between physicians and laboratory professionals.
In late 2010, “bath salts” appeared on the scene in North America and exploded with 6138 human-exposure calls to the US poison control centers in 2011 (1, 2). Although only 1717 cases have been reported to poison control centers as of June 30, 2012, the number of cases has increased for 6 consecutive months (3). Because the American Association of Poison Control Centers database depends on voluntary reporting, the current numbers certainly underestimate the magnitude of the epidemic as emergency physicians become more familiar with bath salt exposures.

The regulatory response by state and federal authorities was much swifter than in previous drug trends. Until we have complete data for 2012, we may not know the full effect of the legal restrictions on bath salts.

From data provided by the US Drug Enforcement Administration, the most frequently seized “bath salts” are mephedrone (4-methyl-N-methylcathinone) and MDPV (3,4-methylenedioxyppyrovalerone). Others include methcathinone (N-methylcathinone), methyleneone (methyleneoxy-N-methylcathinone), and 4-MEC (4-methyl-N-ethylcathinone) (2).

Cathinone derivatives (bath salts) and amphetamine derivatives have strikingly similar 2-dimensional structures, often differing principally in the ketone at the β carbon. Yet, the cathinones tend not to produce positive results in urine screens for amphetamine.

Because advanced laboratory techniques are usually not routinely and rapidly available in most hospitals, the emergency physician may be left in a diagnostic quandary when a patient with apparent sympathomimetic toxidrome (agitation with tachycardia, hyperthermia, and/or hyperthermia) fails to display cocaine metabolites or amphetamines in the urine drug screen. Fortunately, the treatment is similar and usually includes benzodiazepines or antipsychotic tranquilizers, repletion of fluids and electrolytes (especially potassium), and sometimes control of temperature or blood pressure (3).

Randox Toxicology has recently marketed an immunoassay for cathinone derivatives (5), and Ameritox has developed a mass spectrometry test (6). These tests may be useful for emergency physicians and for law enforcement, especially in areas with a high prevalence of bath salt use.