Series Editor: Lewis S. Nelson, MD

Mail Order Madness

Nicholas Connors, MD, and Lewis S. Nelson, MD

A 14-year-old boy has a seizure after smoking a substance he and a friend purchased through the Internet.

Case

A 14-year-old boy suffered a seizure shortly after he and a friend smoked a substance they ordered from an herbal products Web site. His friend called EMS before fleeing from the scene. Upon presentation to the ED, vital signs were: blood pressure, 137/86 mm Hg; heart rate, 143 beats/min; respiratory rate, 20 breaths/min; temperature, 100.0°F. Oxygen saturation was 99% on room air. On physical examination, he was awake, though laughing and making nonsensical word associations. He did not appear to be hallucinating, but did not respond appropriately to questions. Abrasions were noted on his forehead, and the pupils were dilated and reactive. His skin was not flushed, diaphoretic, or dry. With the exception of tachycardia, cardiac, pulmonary, and abdominal examinations were normal. He had no focal motor or sensory deficits or tremor, and motor tone was normal. Initial laboratory values were: finger-stick glucose, 210 mg/dL; sodium, 140 mEq/L; anion gap, 20 mEq/L. An electrocardiogram showed sinus tachycardia at 135 beats/min, with a QRS duration of 80 ms and QTc interval of 453 ms.

What could these boys have taken?

Abused substances that cause agitation, confusion, and central nervous system (CNS) and cardiovascular excitability are numerous and varied. Users of cocaine, amphetamines, and methylxanthines present with symptoms and signs characteristic of the sympathomimetic toxidrome, such as agitation, tachycardia, and hypertension. Additional sequelae of their use include hyperthermia, seizure, dysrhythmia, and ischemia.

Although this patient was somewhat agitated, postictal, and tachycardic, his mental status was suggestive of a dissociative agent such as phencyclidine (PCP), ketamine, or dextromethorphan. PCP use may result in extreme agitation and, at times, violent behavior; ketamine and dextromethorphan produce similar, but more moderate, effects. Dextromethorphan is found in cough and cold preparations and is commonly abused by teenagers due to its accessibility as a nonprescription medication. Herbal products like jimsonweed (*Datura stramonium*), yohimbine (*Pausinystalia yohimbe*), and *Salvia divinorum* are readily available over the Internet but do not generally cause the combination of hyperadrenergic vital-sign abnormalities and CNS effects seen in this case.

Synthetic cannabinoids such as "Spice" (also known as "K2" or "potpourri") and synthetic cathinones ("bath salts") are also available through the Internet because of their uncertain legal status as products labeled, "not for human consumption." In addition to these agents, which have garnered significant media and regulatory attention over the last several years, substituted phenylethylamine derivatives also have potent psychoactive sympathomimetic effects.

Case continuation

When the patient's parents arrived at the ED, they brought a small sheet of blotter paper, thought to be the source of the drug. Few drugs are sufficiently potent enough to be distributed on blotter paper, which requires doses in the microgram range. Examples include LSD, certain tryptamines, and substituted phenylethylamines (4-bromo-2,5-dimethoxyamphetamine; DOB). In this case, the label on the blotter paper suggested the nature of the agent.

What are substituted phenylethylamines?

Phenylethylamines, also generally known as amphetamines, are organic compounds that function as CNS neuromodulators. They have a clinical role as stimulants, psychedelics, antidepressants, decongestants, bronchodilators, and anorectics. The addition of functional groups to the backbone of the phenylethylamine molecule may alter the clinical effects (both psychoactive and sympathomimetic) and pharmacokinetics of these

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drugs. (See the Figure on page 18 for the chemical structure of commonly abused substituted phenylethylamines.) Substitutions along the ethylamine chain tend to enhance the sympathomimetic effects by stimulating the release of catecholamines such as dopamine and norepinephrine from presynaptic neurons. These substitutions make the agent more "speedy." In addition, substitutions on the ring structure improve the effects mediated by the serotonin receptors, making the substance more psychoactive or "trippy." With the substitution of halogens along the ring structure, the agent typically becomes more potent, and only microgram doses are needed to achieve the same "speedy" or "trippy" effects, or a combination of these. Phenylethylamines can be taken orally, intravenously (IV), or through insufflation or inhalation.

The 2C series agents fall into the phenylethymamine class and generally have the core structure of 3,4-methylenedioxy-N-methamphetamine (MDMA, "Ecstasy") with a substituted halogen on the six-carbon ring and methoxy side chains at the 2 and 5 positions on the ring structure. As noted, a halogen typically increases the substance's potency, and the methoxy groups on the ring enhance serotonergic activity, resulting in greater psychoactive affects. Of late, there has been a proliferation of synthetic products that vary slightly in their chemical structure, with resulting unique clinical effects.

The 2,5-dimethoxy-N-(2-methoxybenzyl)phenylethylamine (NBOMe) series of substances are structurally similar to the 2C series but were not widely used before 2010. The mechanism of action involves partial agonism at the $5HT_{2A}$ receptor, resulting in its enhanced "trippy" effect. NBOMe is generally insufflated or applied to blotter paper for buccal absorption. In one cohort, 57% purchased the substance through the Internet, and 83% used it in conjunction with other illicit drugs.[1] The most common subjective effects were changes in tactile, visual, and auditory perception. Trembling, sweating, and blurry vision were the most common adverse effects.[1] Case reports of intoxication with a 2C agent describe recurrent seizures and serotonin toxicity,[2] and fatal toxic leukoencephalopathy[3] noted on magnetic resonance imaging. Effects last about 4 to 8 hours.[4]

What is the legal status of phenylethylamines?

The Controlled Substances Act of 1970 established the Drug Enforcement Agency's (DEA) five "schedules" of substances based on abuse potential, indications for medical use, and safety profile. Schedule I substances have a high potential for abuse and are deemed unsafe even under medical supervision.[5] Drugs such as heroin, lysergic acid diethylamide (LSD), mescaline, and marijuana are on the list of Schedule I substances. Additions to this list include MDMA in 1985, gamma-hydroxybutyrate (GHB) in 2000, and specific synthetic cannabinoids and synthetic cathinones in 2012.

On January 4, 2013, certain substances within the class of 2C drugs were designated Schedule I by the DEA.[6] However, a major difficulty with synthetic agents is the efforts of "street chemists'" to be "one step ahead" of legal authorities. As each specific substance is banned, a derivative or analog is synthesized, avoiding legal prosecution. Furthermore, it is difficult to ban an entire class of agents, and research into potential benefits of

Dr Connors is a fellow of medical toxicology in the department of emergency medicine at the New York University School of Medicine and the New York City Poison Control Center. **Dr Nelson**, editor of "Case Studies in Toxicology," is a 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.

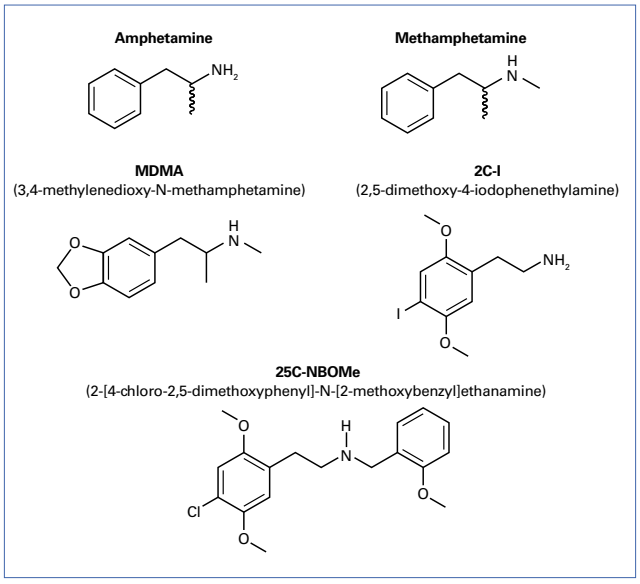

FIGURE Molecular structure of substituted phenylethylamines.

substances can be stifled without significant justification.

The Federal Analog Act of 1986 is an addition to the Controlled Substances Act and addresses issues related to "designer drugs."[7] The wording in this act is vague—perhaps intentionally—with regard to what constitutes an analog, and there has been mixed experience in case law. For example, a federal district court in Colorado ruled that the law was "unconstitutionally vague," making successful prosecution of those who possess or use these substances difficult—especially since these compounds are typically labeled as "not for human consumption," suggesting, almost tongue-in-cheek, that they are not to be abused.[8]

How is phenylethylamine toxicity managed?

After attending to the patient's vital systems, sympathomimetic effects should be treated with rapid-onset benzodiazepines such as diazepam or midazolam. If seizures are refractory to benzodiazepines, propofol, paralysis with a neuromuscular blocker, and intubation should be considered. A core body temperature above 105°F necessitates rapid cooling. For patients with altered mental status and only mild agitation, reducing stimulation as much as possible can be sufficient.

Evaluation should include assessing the patient's electrolytes to screen for hyponatremia (common with certain ring-substituted amphetamines) and other causes of seizure. Measuring creatine kinase to assess for rhabdomyolysis should be considered if there a history of prolonged immobilization or severe hyperthermia. Noncontrast computed tomography (CT) of the head can be performed in cases of altered mental status, particularly if there was head trauma or concerns for subarachnoid bleeding. Patients should be observed until symptoms abate and then discharged home, as appropriate, after evaluation for suicidality along with counseling on the dangers of drug use and possible referral for drug treatment.

Case conclusion

The patient received multiple doses of IV diazepam for sedation. Upon waking the next day, he stated that he used 25C-NBOMe (2-[4-chloro-2,5-dimethoxyphenyl]-N-[2-methoxybenzyl]ethanamine; also called "Pandora," "Dime," "Vortex," "Cimbi-82") on blotter paper for the first time on the day of presentation. He added that he and his friend had ordered the drug from a synthetic-product Web site that advertised the substance as "legal LSD."

The patient was admitted to the hospital for further testing. He had a normal noncontrast CT of the head, and anion gap narrowed to within normal parameters. He was observed overnight in the pediatric intensive care unit where his vital signs normalized. He was discharged the next day without report of sequelae.

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