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CASE REPORT

Julia C. Drees,[1] *Ph.D.; Judy A. Stone,*[1,2] *Ph.D.; and Alan H. B. Wu,*[1,2] *Ph.D.*

Morbidity Involving the Hallucinogenic Designer Amines MDA and 2C-I*

ABSTRACT: A case is presented of a 39-year-old woman who suffered severe debilitation because of a hemorrhagic stroke in the context of substance abuse. The patient presented to the emergency room with rapidly diminishing mental status, hypertension, and vasoconstriction; her friends provided a history of ingestion of cocaine, 3,4-methylenedioxymethamphetamine (MDMA), and 2C-I, a novel designer amine. A multi-targeted LC-MS/MS method for sympathomimetic amines and related drugs in urine detected and quantified 2C-I and MDA, while ruling out MDMA. The cause of the stroke was determined to be an underlying cerebrovascular abnormality called Moyamoya, secondary to substance abuse. In clinical laboratories, gas chromatography–mass spectrometry or liquid chromatography–tandem mass spectrometry (LC-MS/MS) confirmation of a positive amphetamine immunoassay is usually directed only towards amphetamine, methamphetamine, MDMA and MDA. This report demonstrates the utility of testing for a wider menu of compounds using LC-MS/MS in order to better characterize the prevalence and toxicities of novel amines such as 2C-I.

KEYWORDS: forensic science, 2C-I, MDA, liquid chromatography–tandem mass spectrometry, hemorrhagic stroke, Moyamoya

The 2C* family of designer amines are derivatives of the natural compound β-phenethylamine (1). They contain methoxy groups in positions 2 and 5 and a hydrophobic 4-substituent, i.e., iodine in 2C-I, bromine in 2C-B (Fig. 1C, inset). The name "2C" comes from the two carbon atoms that separate the amine from the phenyl ring. The 2C* drugs have hallucinogenic properties and are sometimes incorrectly sold as 3,4-methylenedioxymethamphetamine (MDMA; "ecstasy") (2). Little is known about the pharmacological and toxicological properties of the 2C* drugs, but their affinity to type-2 serotonin (5-HT2) receptor has been demonstrated, acting as agonists or antagonists similarly to other hallucinogenic drugs (3). The synthesis of 2C-I was published in 1991 (1) and the drug became popular in tablet form as a club drug in the United Kingdom around 2003.

The psychotropic amphetamine 3,4-methylenedioxyamphetamine (MDA, Fig. 1B, inset) is also derived from phenethylamine. MDA is a minor metabolite of the more widely used MDMA but it also has its own long history as an independently used drug. MDA was first synthesized in 1910 and became popular for recreational use starting in the 1960s (4). Like the 2C* drugs, it is also sometimes incorrectly sold as "ecstacy" in tablet form (5). Some reports indicate that MDA may have more potent effects than MDMA (6).

Moyamoya is a cerebrovascular abnormality manifesting in the formation of a network of new blood vessels. This formation results from decreased blood flow because of the obstruction of the two main brain vessels and patients with Moyamoya have an increased risk for stroke. Several case reports link drug-related intracranial hemorrhages with underlying vascular malformations (7,8). The drugs cited include cocaine, amphetamine, and MDMA, and the patients are typically young with nontraumatic hemorrhagic stroke. Mortality and morbidity are noted to be higher in the drug-related cases.

[1]Department of Laboratory Medicine, University of California—San Francisco, San Francisco, CA.
[2]Clinical Laboratory, San Francisco General Hospital, San Francisco, CA.
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Case History

A 39-year-old African-American woman presented to the emergency department on New Year's day after a night of partying. The patient exhibited rapidly diminishing mental status, agitation, hypothermia, emesis, urinary incontinence, severe hypertension, vasoconstriction, and extensor posturing. Her friends provided a history of alcohol, cocaine, MDMA, and 2C-I ingestion sometime between 2300 the night before and 1100 on the day of admission. The patient reportedly synthesized the 2C-I at home using a recipe from the internet. Toxicology testing was ordered on a patient urine sample that was collected 1 h after admission at 1400.

A head CT scan diagnosed a massive intraventricular hemorrhage and a cerebral angiogram revealed underlying Moyamoya. Neurosurgery placed an external ventricular drain as well as a ventriculoperitoneal shunt. After 1 month, the patient developed sympathetic storming, occasionally triggering seizures. The patient required mechanical ventilation during the majority of her prolonged hospitalization, eventually requiring placement of a tracheostomy. After 4 months in and out of the ICU, the patient was discharged to a skilled nursing facility with quadriplegia and only a modest improvement in mental status. The patient could follow simple commands but not speak; she remains severely disabled and requires total care.

Materials and Methods

Only one urine sample collected in the emergency department 1 h after admission was available for testing. The patient urine was screened for amphetamines, barbituates, benzodiazepines, cocaine metabolite, methadone metabolite, opiates, and oxycodone using competitive, homogenous immunoassays (CEDIA/DRI—

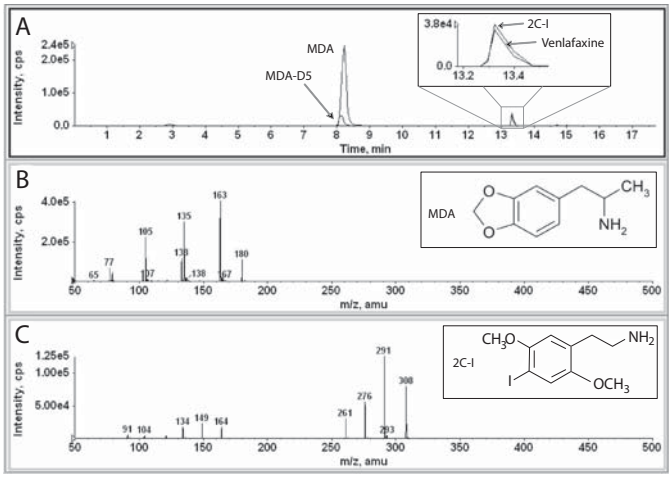

FIG. 1—*LC-MS/MS analysis of the patient's urine sample, identifying the presence of MDA and 2C-I. The extracted ion chromatogram of the survey scan (A) and the product ion spectra for MDA (B) and 2C-I (C) are shown. Insets: (A) Expanded view of 2C-I and venlafaxine. (B) Chemical structure of MDA. (C) Chemical structure of 2C-I.*

Microgenics [Fremont, CA] on an Adiva 1800 by Bayer [Leverkusen, Germany]).

Amphetamine confirmation was performed using high performance liquid chromatography (HPLC) coupled with rapid UV scanning (REMEDi by BioRad, Hercules, CA) and subsequently using liquid chromatography–tandem mass spectrometry (LC-MS/MS; 3200 QTrap® from Applied Biosystems, Foster City, CA). The multi-targeted LC-MS/MS method was developed in-house to detect drugs that can cause sympathomimetic syndrome and related drugs, including designer amines such as 2C-I. For LC-MS/MS methods, urine was diluted 1:10 with 10 mM ammonium formate, pH 3.0 and spiked with internal standards. The method did not include hydrolysis. MDA-D5 was used for MDA and venlafaxine was chosen as an internal standard for 2C-I since it elutes at the same retention time. All reagents were from Fisher Scientific (Pittsburgh, PA) and all standards were from Cerilliant (Round Rock, TX) except 2C-I, which was from Lipomed (Cambridge, MA). Separation occurred on a Waters (Milford, MA) XTerra MS C18, 3.5 um (100 × 2.1 mm) column at 25°C with a gradient of mobile phase A (pH 3.0, 0.5 mM ammonium formate) and mobile phase B (acetonitrile:pH 3.0, 10 mM ammonium formate; 90:10 by volume). The flow rate was 300 µL/min and the program was: 0–8 min, 5% to 15% B; 8–14 min, 15% to 60% B; 14 to 15 min, 60% to 5% B; 15–18 min, equilibration with 5% B. With this program, MDA eluted at 8.3 min and 2C-I eluted at 13.3 min. The ion transitions used were 180/163 (MDA), 185/168 (MDA-D5), 308/291 (2C-I), and 278/58 (venlafaxine). Mass spectrometry was in the positive mode using electrospray ionization.

For identification of the drugs in the sample, the LC-MS/MS method used an information-dependent acquisition (IDA) strategy. IDA was configured in the Analyst 1.4.2 software (MDS Analytical Technologies, Toronto, Ontario, Canada) using selected reaction monitoring for 18 precursor:product ion transitions as a survey scan, followed by product ion scans generated in Q3 functioning as a linear ion trap. Product ion scans were generated when IDA criteria were met (detection of a peak <7000 cps). An automated library search of all acquired product ion spectra was performed and a match factor (purity) of 70% or greater between the unknown and library product ion spectra was required to report a drug as positive. In addition, the ion ratio for MDA must be within 20% of the cutoff calibrator (0.5 mg/L). Ion ratios were not evaluated for 2C-I since full scan product ion spectra were used for identification instead of product ion ratios. For quantitation, the peak area ratios of the drugs to the internal standards were compared with a standard curve.

For MDA, the assay was linear from 0.10 to 6.5 mg/L, the within-run imprecision (CV) was <5% (n = 5) (controls at 0.35 and 0.60 mg/L) and the between-run imprecision was <7% (controls at 0.45 and 0.65 mg/L) (n = 118). The LOQ was 0.10 mg/L and the LOD was not determined. For 2C-I, the assay was linear from 0.05 to 2.5 mg/L (r = 0.996) and the within-run imprecision was <10% for controls run in duplicate at 0.05, 0.5, 1.0, and 2.5 mg/L. The accuracy of a positive control at 0.25 mg/L was 92.5% based on the weighed-in value, and the signal-to-noise ratio for the 0.05 mg/L standard was >50. Between-run precision, LOD, and LOQ were not determined for 2C-I since this is the only time it has been detected in our laboratory.

Results and Discussion

Ethanol tests were not ordered. The immunoassay screen of the patient's urine was preliminary positive for amphetamines, which triggered a confirmation test. The amphetamine screen was found to have no cross-reactivity with 2C-I (up to 100,000 ng/mL spiked into drug free urine). The screen was negative for all other drugs, including cocaine metabolite, which is inconsistent with the history provided by the patient's friends. This suggests that the patient or the friends were not completely aware of or knowledgeable about the drugs they were using. The HPLC scanning UV method used for amphetamine confirmation was negative for amphetamine and methamphetamine and an interfering substance prevented the detection of MDMA and MDA. However, a multi-targeted LC-MS/MS method was able to detect and quantify both MDA (at a concentration of 5.56 mg/L) and 2C-I (0.311 mg/L) in the patient's urine (Fig. 1). The dose–toxicity relationship of 2C-I is unknown; however, this level is approximately two times higher than the highest concentration nonhydrolyzed urine from five habitual consumers of designer drugs in a study where urine was collected a few hours after drug ingestion (9). Therefore, it is possible that the concentration of 2C-I detected in the patient was toxic and contributed to the patient's symptoms. Additionally, the concentration measured was likely not the maximum given the potentially long time period between ingestion and urine collection (up to 15 h). It is important to note that the method used only detects parent drug, but 2C-I is known to be present in conjugated and metabolized forms in urine (9,10).

While it is possible that the MDA in the patient sample is residual from a remote MDMA exposure, the fact that no MDMA was detected by LC-MS/MS suggests that the patient ingested MDA and not MDMA, as was stated in the history. This is the first time MDA has ever been detected in the absence of MDMA in our laboratory even though over 11,000 urines are screened per year, and approximately 7% and 0.5% are confirmed positive for methamphetamine and MDMA, respectively. In one documented MDMA fatality, urine concentrations of MDMA and MDA were 171 and 4 mg/L, respectively (11). The amount of MDA detected in this patient sample is within the range of the urine concentrations in 12 recorded MDA fatalities (2–175 mg/L; average 108 mg/L MDA) (11). A syndrome of hypertension, tachycardia, mental status changes, and cardiovascular accidents following MDMA ingestion has been well described (12). Similar reports are less common for MDA (11) and nonexistent for 2C-I, perhaps because such exposures are less common, or at least less often identified.

In conclusion, the 2C-I exposure documented for this patient may have been coincidental or may have been contributory to the hypertensive episode and subsequent stroke associated with an MDA (or possibly MDMA) ingestion and underlying Moyamoya. A surprising variety of toxic presentations thought to be caused by exposure to MDMA alone have been described: serotonin syndrome, severe psychiatric disorders, multi-organ failure, malignant hyperthermia, hepatitis, and rhabdomyolysis (12). Use of a method for a broad menu of 18 over-the-counter, prescription, and illicit sympathomimetic amine compounds using LC-MS/MS allowed the detection of this unusual co-ingestion which would have been missed by more narrowly targeted techniques. There is a lack of published data on the clinical scenario of morbidity because of the presence of 2C-I or 2C-I and MDA together. Additionally, understanding of the prevalence and toxicities of these drugs is limited. Widespread use of multi-targeted LC-MS/MS methods and reporting of quantitative findings may help to clarify the prevalence, and better characterize the toxicities, associated with the designer amines.

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Additional information and reprint requests:
Alan H. B. Wu, Ph.D.
Department of Laboratory Medicine
University of California—San Francisco
San Francisco, CA
E-mail: wualan@labmed2.ucsf.edu