

Research Article

Open Access

Alarming Trends in a Novel Class of Designer Drugs

Owen Mc Grane*, Joshua Simmons, Eric Jacobson and Carl Skinner

Department of Emergency Medicine, Madigan Army Medical Center, Tacoma, WA, USA

Abstract

Recent years have shown an increase in the use of the so-called “designer drugs.” This term is usually applied to recreational drugs that are new, synthetic and emerge as unscheduled drugs since they have not been in existence long enough to be illegal. These drugs are usually available at “head shops”, tobacco stores, gas stations and via the internet. Several such classes have gained increasing notoriety in the past 3-4 years, especially Spice and bath salts. One class that has gone almost unrecognized is the 2C class.

The 2C's are a class of synthetic hallucinogens known as phenethylamines, the same class as the naturally occurring drug mescaline. Few case reports of actual overdoses from 2C compounds have been reported, but some of the physical stigmata of use or overdose are thought to be pupil dilation, facial flushing, diaphoresis, bruxism, facial grimacing, tachycardia, tachypnea, emotional lability, and subjective symptoms such as accelerated internal clock, and detachment from surroundings. There are no known screening tests to easily detect the substance. However, it has been shown to be detected in rat urine using gas-chromatographic-mass spectrometry (GM-MS) as well as in human blood plasma using gas chromatography-mass spectrometry (GC-MS) and in human urine by capillary electrophoresis-MS [11,23]. Recommended treatment is similar for treatment of most hallucinogenic or sympathomimetic overdoses, and includes supportive care, benzodiazepines, and placing patient in a calm, quiet setting. Use of SSRI for “bad trips” has been described in the lay literature, but is not recommended [20].

Introduction

With three deaths and twenty patients hospitalized, the spring of 2011 had an alarming trend of overdoses from a relatively unknown group of designer drugs [1-4]. The drugs responsible are analogs from the 2,5-Dimethoxy phenethylamine drug class, more commonly known as the 2C series. These synthetic hallucinogens are in the same class as the naturally-occurring drug mescaline (peyote). They are gaining popularity as rave drugs and readily available over the internet, in “head shops,” tobacco stores and even gas stations [1]. Though they have been regarded as relatively safe, there are multiple case reports that detail their possible life threatening adverse reactions, and abuse potential [1-4]. Several other classes of designer drugs to include synthetic cannabinoids (Spice) and congeners of cathinone (bath salts) have gained increasing notoriety in the past three to four years, though the 2Cs have gone almost unrecognized by many primary care medical providers, as well as law enforcement. 2Cs can cause vivid and intense hallucinations, over-stimulation, agitation, seizures and hyperthermia [1,5-7]. Most commonly found as a white crystalline powder, it can be taken orally through tablets or capsules, insufflation as a powder, or even anecdotally used intravenously [5]. It is believed to be first synthesized by Alexander Shulgin, a well-known American born chemist and pharmacologist that has been credited with discovering and synthesizing over 230 psychoactive compounds. In his book “PiHKAL: A Chemical Love Story,” he describes the synthesis, dosage, and duration of action for the 2Cs as well as extensions and qualitative commentary on their usage and subsequent effects [5]. He refers to this group as the “magical half dozen” that includes 2C-B, 2C-E, 2C-T-7, 2C-T-2, DOM, and Mescaline [5]. 2C-E and 2C-T-2 are unscheduled in the United States, however as an analog of 2C-B, 2C-T-7 and mescaline which are scheduled substances, their sale for human consumption or possession to ingest for illicit purposes could be prosecuted as crimes under the Federal Analog Act [8].

Pathophysiology

The first synthetic hallucinogen type drug was lysergic acid diethylamide, or LSD, initially marketed as an anesthetic and adjunct to psychoanalysis. LSD emerged as a recreational drug in the 1960's,

but was banned under US law in 1966. Mescaline, which is a naturally occurring derivative of the 2Cs, produces hallucinogenic effects similar to LSD, but on a milder scale. It continues to be used for religious ceremonies by members of the Native American Church. These drugs cause hallucinations in which a person experiences sensory perceptions in absence of stimuli. The desired effects include heightening of sensory and enhancement of emotions, feelings and introspection. They also cause mild sympathomimetic effects of tachycardia, hypertension, hyperthermia, diaphoresis, and sometimes nausea and vomiting.

The basic structure of the 2C compounds is a phenethylamine backbone with two methoxy groups at positions 2 and 5 of the aromatic ring with various lipophilic substituents at the 4 position [10] (Figure 1). This particular structure is thought to be responsible for the hallucinogenic effect of these compounds [11]. Multiple substitutions at the number 4 position have proven to have hallucinogenic effects, with the most popular being a bromide group (2C-B), an ethyl group (2C-E), an Iodine group (2C-I) and a propyl group (2C-T2 and T7) (Figure 1). The exact mechanism of these substances is unknown; however, they show affinity for the 5-HT₂ serotonergic receptor [10-12] and acts as an agonist or antagonist at the various receptor subtypes [11-13]. In rats, partial agonism of β -1 adrenergic receptors has also been described in 2C-B [14,15].

From animal and human studies, the 2C compounds are mainly metabolized by the phase I reactions O-demethylation(at position

*Corresponding author: Owen Mc Grane, Department of Emergency Medicine, Madigan Army Medical Center, Tacoma, WA, USA, E-mail: omcgrane@gmail.com

Received November 05, 2011; Accepted November 14, 2011; Published November 16, 2011

Citation: Grane OM, Simmons J, Jacobson E, Skinner C (2011) Alarming Trends in a Novel Class of Designer Drugs. J Clin Toxicol 1:108. doi:10.4172/2161-0494.1000108

Copyright: © 2011 Grane OM, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

2 or 5 of the phenol ring) and/or deamination to its corresponding aldehyde. The aldehyde from deamination is then reduced to its alcohol or oxidized to a carboxylic acid. Most likely due to its structural similarity to dopamine and norepinephrine, the deamination reaction is done primarily by monoamine oxidase (MAO)-A and to a lesser extent MAO-B enzymes [11,16]. Phase II reactions included partial glucuronidation or sulfation and N-acetylation [11,16].

Epidemiology

The 2C series of synthetic drugs of abuse were first synthesized and described by Alexander Shulgin in the 1970s and 80s. They gained popularity in the 1990s after the publication of his book PiHKAL [5]. The first of the 2C compounds to appear in the market was 4-bromo-2,5-dimethoxy-β-phenethylamine (2C-B) in the mid-1980s [1]. This was followed by the S-alkyl compounds 4-ethylthio-2,5-dimethoxy-β-phenethylamine (2C-T-2) and 2,5-dimethoxy-4-propylthio-β-phenethylamine (2C-T-7) [1]. In the mid-1990s, 4-iodo-2,5-dimethoxy-β-phenethylamine (2C-I) appeared [1]. As older compounds began to be regulated as scheduled substances, slight modifications were made to compounds to allow their continued sale. These compounds are sold primarily on the internet and in shops that specialize in drug paraphernalia (i.e. 'smoke shops', 'head shops', 'smart shops'). They are sold in tablet, liquid and liquid preparations and may also be mixed with other drugs [1].

Legislation

In 2009, the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), identified several 2C compounds as synthetic psychoactive substances of concern for their abuse potential [17]. In the United States, the Federal Analogs Act addresses analogs of controlled substances [8]. Though these analogs are not themselves classified as controlled substances, they are "substantially similar," either structurally or pharmacologically, to a Schedule I or II controlled substance and are intended for human consumption [8]. The Act is controversial and is considered largely ambiguous due to its' wording. For example, there is no definition to how similar the structure has to be in order to be considered "substantially similar," as well as how similar the pharmacologic effects have to be to that of a controlled substance. Also in regards to being intended for human consumption,

it is unclear where the burden of proof lies, with the defendant having to prove that the substance was not for human consumption, or with the prosecution having to prove that the substance was for human consumption. This vague wording has made the Federal Analog Act difficult for both lawyers and judges to interpret and prosecute under [18,19].

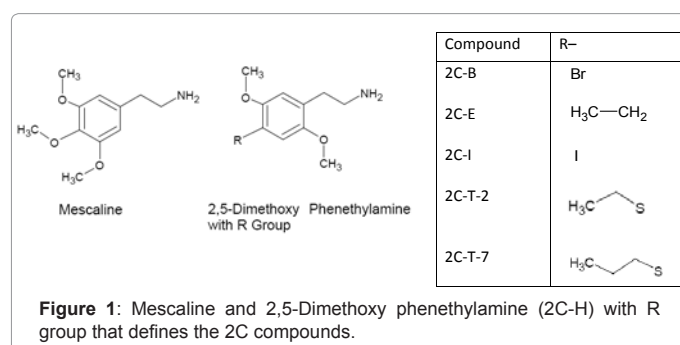
Clinical Manifestations

In Shulgin's book, he describes his experiences with varying dosages of the 2C compounds. At the lower range, he reports primarily euphoria and visual hallucinations. At higher dosages, he reported anxiety, tremors and auditory hallucinations. The commonly used oral dose range for this group of drugs is anywhere from 10–25 mg with a reported onset 20 min, a peak of 2 hrs, and a duration 6–12 hrs. According to Shulgin, perception may be somewhat altered for up to a day after ingestion. He describes reports of users ingesting up to 100mg describing effects lasting greater than 24 hours and with higher doses, that perception may be somewhat altered for up to a day after ingestion [5].

Several lay sites, such as Erowid and drug forum confirm Shulgin's assertions about the 2C compounds. These sites are purported to be safe use of illicit drugs and provide information about the dose, manifestations and side effects. They describe the 2C's as being unique for heightened synesthesia, as well as less emotional and psychedelic heightening effects, and more pronounced thought clarity and introspection [20]. Reported symptoms of 2C ingestion include midriasis, facial flushing, increased perspiration, bruxism and facial grimacing, tachycardia, tachypnea. Psychiatric symptoms include emotional lability, alterations in perception of time and unawareness of surroundings [5,17,20,21].

Few deaths or adverse effects have been reported with this class of drug. One documented death recently occurred in the town of Blaine, MN. A 19 year old male, as well as 10 others, was allegedly using 2C-E at a party with some friends when he was reported by witnesses to have become combative, shouting nonsensically, and eventually collapsed and stopped breathing. He was taken to the local hospital where he was maintained on life support but care was eventually withdrawn [3,4]. Several news articles have reported that his BAL was less than 0.06%, and no other drugs were found in his blood, but no details were given as to his clinical presentation or what drug assays were used [3,4]. There were two other deaths reported recently in Seminole, OK as well as six others requiring hospitalization initially thought to be from 2-CE, however after chemical analysis the actual substance is believed to be another powerfully-hallucinogenic 2C analog known as 2C-B (Bromo-DragonFLY) [3].

We found three cases that were reported to the Washington State Poison Center of 2C exposures. A 17 year old male with a history of bipolar disorder was found agitated and combative in a hotel after reportedly taking 2C-B in liquid form. His reported medications are lithium, Adderall (amphetamine and dextroamphetamine), levothyroxine, bupropion and tetracycline. When EMS arrived, the patient was very agitated and he was given lorazepam IV. After three 1 mg doses, he was intubated secondary to continued agitation. His reported heart rate was 75 and his blood pressure was 90 systolic. Initial laboratory tests were remarkable for a urine drug screen positive for amphetamines and marijuana. Alcohol, aspirin level and acetaminophen level were negative. His lithium level was therapeutic. His creatinine was elevated at 1.7mg/dL. The patient was maintained on a propofol drip for sedation until he was cooperative enough for extubation, which was approximately 10 hours later. He had some



Compound	Street Names
Mescaline	Peyote, Buttons, Mesc
2C-B	Nexus, 2's, Toonies, Bromo, Spectrum, Venus
2C-E	Europa, Tootsie
2C-I	I, Izzy, Isabel
2C-T-2	Rosy
2C-T-7	Blue Mystic, T7, Beautiful, Tripstay, Tweety-Bird Mescaline

Table 1:

residual confusion that resolved over the next 24 hours and then was discharged the next evening.

A second case is a 25 year old male also with a history of bipolar disorder who was witnessed taking 4-5 aripiprazole 10mg tablets, a 1.5 ounce shot of alcohol and snorted an unknown amount of 2C-I in a suicide attempt. The patient was awake and interactive on EMS arrival. He was transported to a local ED, where he was treated symptomatically with IV fluid therapy and was discharged after a period of observation. His alcohol, aspirin, acetaminophen levels were all normal. His lithium level was within therapeutic range.

A third case that was called in to the Washington Poison Center is a 15 year old female with known insulin-dependent diabetes mellitus who presented the morning after going to a rave where she ingested one tab of Ecstasy (MDMA) and one tab of 2C-B. She started vomiting sometime after midnight and presented to a local ED with abdominal pain and vomiting. Her blood sugar was 500 mg/dL initially. Initial vital signs were remarkable for a heart rate in the 120s, blood pressure of 111/61 and a respiratory rate of 31 breaths per minute. Her blood pH was 7.15. She had a sodium of 138 mg/dL, potassium of 3.9 mEq/dL, chloride of 111 mg/dL, calcium of 8.3 mg/dL and a phosphate of 2.4 mg/dL. She was treated for diabetic ketoacidosis with IV fluids and insulin and was discharged 2 days later.

Diagnostic Evaluation

There are currently no known screening tests to easily detect the substance. However, it has been shown to be detected in rat urine using gas-chromatographic-mass spectrometry (GC-MS) [22]. 2C-E has been detected in human blood plasma using gas chromatography-mass spectrometry (GC-MS) and in human urine by capillary electrophoresis-MS [11,23]. Using systematic toxicological analysis (STA) in a rat model, 2C-E was found to be extensively metabolized. The primary detected compounds in the urine were found to be the *N*-acetyl-*O*-dimethyl and *N*-acetyl-*O*-dimethyl-oxo metabolites, as well as acetylated 2C-E [11]. The authors suggest this as a possible way to screen for 2C-E abuse in human urine [11].

Treatment

Expected effects from using the 2-C compounds include psychiatric manifestations and autonomic instability to include tachycardia, hypotension, diaphoresis, and hallucinations. There have been no studied unique treatments for these compounds. Recommended treatment might include supportive care, benzodiazepines, and placing patient in a calm, quiet setting. Clinicians who are treating patients with intoxication of the 2-C compounds are encouraged to seek help from a medical toxicologist or personnel of their poison control system.

Acknowledgements

We thank William Hurley, MD and the Washington Poison Center for providing the above case reports.

References

- de Boer D, Bosman I (2004) A new trend in drugs-of-abuse; the 2C-series of phenethylamine designer drugs. *Pharm. World Sci* 26: 110.
- 2C-B (Nexus) reappears on the club drug scene. *Information Bulletin US Department of Justice*, product no. 2001-L0424-002, DEA 2001.
- Louwagie P (2011) New Drugs Full Wave of violence and Death. *Minnesota StarTribune*.
- Chanen D (2011) Blaine man arrested after overdose at house party. *Minnesota Star Tribune*.
- Shulgin A, Shulgin A (1991) *PIHKAL: A chemical love story*. Berkeley, California: Transform Press.

- Schifano F, Deluca P, Agosti L, Giovanni Martinotti, John M. Corkery (2005) New trends in the cyber and street market of recreational drugs? The case of 2C-T-7 ('Blue Mystic'). *J Psychopharm* 19: 675-679.
- Sanders B, Lankenau SE, Bloom JJ, Dodi Hathazi (2008) "Research Chemicals": Tryptamine and Phenethylamine use among high-risk youth. *Subst Use Misuse* 43: 389-402.
- Federal Analog Act. Title 21 U.S. Code Chapter 13 Subchapter I Part A § 802, 2010.
- Theobald DS (2006) The 2C-series – A new Class of Designer Drugs: Studies on the Identification of Metabolites, and Toxicological Analysis as well as on Cytochrome P450 and MAO Isoforms Involved in Major Metabolic Steps. *Universität des Saarlandes*.
- Monte AP, Marona-Lewicka D, Parker MA, Wainscott DB, Nelson DL, Nichols DE (1996) Dihydrobenzofuran analogues of hallucinogens. 3. Models of 4-substituted (2,5-dimethoxyphenyl)alkylamine derivatives with rigidified methoxy groups. *J Med Chem* 39: 2953.
- Theobald DS, Maurer HH (2006) Studies on the metabolism and toxicological detection of the designer drug 4-ethyl-2,5-dimethoxy- β -phenethylamine (2C-E) in rat urine using gas chromatographic-mass spectrometric techniques. *J Mass Spectrom* 41: 1509-1519.
- Glennon RA, Raghupathi R, Bartyzel P, Teitler M, Leonhardt S (1992) Binding of phenylalkylamine derivatives at 5-HT_{1C} and 5-HT₂ serotonin receptors: evidence for a lack of selectivity. *J Med Chem* 35: 734.
- de Boer D, Gijzels MJ, Bosman IJ, Maes RA (1999) More data about the new psychoactive drug 2C-B. *J Anal Toxicol* 23: 227-228.
- Saez P, Borges Y, Gonzalez E, Cassels BK (1994) Alpha-adrenergic and 5-HT₂-serotonergic effects of some beta-phenylethylamines on isolated rat thoracic aorta. *Gen Pharmacol* 25: 211-216.
- Lobos M, Borges Y, Gonzalez E, Cassels BK (1992) The action of the psychoactive drug 2C-B on isolated rat thoracic aorta. *Gen Pharmacol* 23: 1139-1142.
- Maurer HH (2010) Chemistry, Pharmacology, and Metabolism of Emerging Drugs of Abuse. *Ther Drug Monit* 32: 544-549
- European Monitoring Centre for Drugs and Drug Addiction (2010) *The State of Drug Problems in Europe*: Luxembourg.
- SA v. Damon S. Forbes et al. (1992) 806: 232
- USA v Washam (2002) 312: 926-930
- Erowid 2C-E (2CE) Vault (2011) www.erowid.org/chemicals/2ce/2ce.shtml.
- Drug Forum 2C-E (2011) <http://www.drugs-forum.com/forum/showwiki.php?title=2C-E>.
- Curtis B, Kemp P, Harty L, Choi C, Christensen D (2003) Postmortem identification and quantitation of 2,5-dimethoxy-4-n-propylthiophenethylamine using GC-MSD and GC-NPD. *J Anal Toxicol* 27: 493.
- Boatto G, Nieddu M, Pirisi MA, Dessi G (2007) Simultaneous determination of new thioamphetamine designer drugs in plasma by capillary electrophoresis coupled with mass spectrometry. *Rapid Commun Mass Spectrom*. 21: 3716-3720.

Submit your next manuscript and get advantages of OMICS Group submissions

Unique features:

- User friendly/feasible website-translation of your paper to 50 world's leading languages
- Audio Version of published paper
- Digital articles to share and explore

Special features:

- 200 Open Access Journals
- 15,000 editorial team
- 21 days rapid review process
- Quality and quick editorial, review and publication processing
- Indexing at PubMed (partial), Scopus, DOAJ, EBSCO, Index Copernicus and Google Scholar etc
- Sharing Option: Social Networking Enabled
- Authors, Reviewers and Editors rewarded with online Scientific Credits
- Better discount for your subsequent articles

Submit your manuscript at: www.omicsonline.org/submission/

