The Ketamine Analog Methoxetamine: A New Designer Drug to Threaten Military Readiness

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ABSTRACT Recent years have seen the emergence and proliferation of "legal highs" or "designer drugs," compounds purposefully designed as legal alternatives to controlled substances of abuse. This article describes methoxetamine, a dissociative drug belonging to the arylcyclohexylamine class including phencyclidine and ketamine. Methoxetamine acts principally on the glutamatergic *N*-methyl-D-aspartate receptor and the serotonin receptor. It is sold as a white or off-white powder. Marketed as a "bladder friendly" alternative to ketamine, preliminary research suggests renal and cystic toxicity similar to ketamine. Methoxetamine is primarily ingested nasally, though also orally, intramuscularly, intravenously, and rectally. Users report dissociative features and, at higher doses, an "m-hole" experience akin to ketamine's "k-hole" described as extreme depersonalization and derealization. The 13 cases of acute methoxetamine toxicity described in the literature are summarized. The toxidrome consists of dissociation/delirium, sympathetic activation, and cerebellar symptoms. Methoxetamine is not detected in standard urine drug tests and there are no reliable laboratory findings. Management of acute methoxetamine toxicity is supportive, consisting of benzodiazepines, antiemetics, intravenous fluids, and respiratory support as indicated. Should methoxetamine conform to the observed 2-year lag of designer drugs migrating from Europe to the United States usage may increase in early 2014.

INTRODUCTION

Recent years have seen the emergence of a proliferation of "legal highs" or "designer drugs," compounds purposefully designed as legal alternatives to controlled substances of abuse. These compounds are created by chemists who intentionally modify the structure of banned substances to produce analogs that circumvent existing laws while producing similar subjective effects.[1]

"Spice," synthetic cannabinoid agonists, and "bath salts," synthetic cathinones, have been but the two most prominent recent legal highs. Both spice and bath salts emerged approximately 2 years earlier in the United Kingdom and Continental Europe than in the United States.[1–3] To anticipate the next wave of legal highs, we propose it may be prudent to look overseas. One such candidate drug is methoxetamine.

Methoxetamine was first identified in the United Kingdom in November 2010.[4,5] Although prevalence remains unknown, United Kingdom poison control center (PCC) calls peaked in the spring of 2012.[6] In the United States, case reports and drug enforcement agency seizures have begun.[7–9] The first case report from the United States describing methoxetamine toxicity was published in August 2011.[7] At present, there is no data concerning the prevalence of methoxetamine use in the United States. However, should it follow a similar 2-year lag time observed with spice and bath salts, methoxetamine use can be expected to rise in 2014. Methoxetamine is currently not controlled under the U.S. Controlled Substances Act, as was the case with spice and bath salts initially.

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In this article, we begin by situating methoxetamine within the broader history of dissociative drugs. We discuss what is known of its origin. Next, we describe the pharmacology of methoxetamine and the clinical presentation of methoxetamine toxicity. We conclude by addressing concerns specific to the U.S. military.

THE EVOLUTION OF DISSOCIATIVE DRUGS

Methoxetamine is a dissociative anesthetic belonging to the arylcyclohexylamine class that includes phencyclidine (PCP) and ketamine.[10] Dissociative drugs, as they are commonly referred to when used as substances of abuse, share the prominent subjective effects of depersonalization, an "alteration in one's experience and awareness of the self, leading to feelings of being unreal or detached from one's own body," and derealization, where individuals "feel that the world around them has suddenly become unreal."[10,11]

PCP, the progenitor dissociative anesthetic, was first synthesized in Germany in 1926.[12] PCP was patented in 1953 and marketed as the general anesthetic Sernyl.[13] PCP did not elicit respiratory and cardiovascular suppression observed with other general anesthetics.[13] The early 1960s saw clinical reports of intraoperative agitation and hallucinations, with psychotic symptoms persisting up to 10 days.[13] Removal from the market in 1965 was contemporaneous with PCP's emergence as a substance of abuse.[13] In the late 1970s, illicit PCP consumption soared in the United States with use by an estimated 15% of those aged 18 to 25 years.[13]

As the untoward effects of PCP were becoming more widely recognized, Dr. Calvin Stevens, an American pharmacist working for Parke-Davis/White (now Pfizer), began researching alternatives. In 1962, he synthesized ketamine.[14,15] The first reported case of use as a recreational drug was in

1965.[14,15] On the street, ketamine became known as "mean green" and "rockmesc."[16] It was approved for human use in the United States in 1970, quickly gaining popularity as a battlefield anesthetic in the Vietnam War.[14] In 1978, Marcia Moore and Howard Alltounian wrote Journeys into the Bright World extolling the existential richness of ketamine-induced dissociative experiences.[17] By the late 1980s, ketamine had resurfaced in the underground rave scene where it was commonly mixed with 3,4-methylenedioxy-N-methylamphetamine (MDMA, ecstasy) and referred to as "dud pills."[15,16] By the early 1990s, ketamine had entered mainstream dance culture.[16] Soon after, in 1999, ketamine was classified as a schedule III controlled substance in the United States with the United Kingdom and Canada, among other countries, soon following suit.[18]

Currently, the FDA approved indications for ketamine use in humans is limited to anesthesia in diagnostic and surgical procedures.[19] At present, there is a flurry of medical research exploring novel uses of ketamine. The role of ketamine in multiple pain conditions is being actively explored.[20] Studies with subanesthetic dosing have shown a rapid antidepressant effect in treatment-resistant unipolar depression.[21] Ketamine use in treatment-resistant bipolar depression also shows promise.[21] These same studies have identified rapid antisuicidal effects.[21] In detoxified heroin addicts, subanesthetic doses of ketamine are associated with longer periods of abstinence, diminished cravings, and reduced depression and anxiety.[22] In the wake of these exciting findings, investigation into ketamine and analogs has begun in earnest.[21]

Clandestine production of ketamine analogs for illicit consumption has also begun, with methoxetamine but the most prominent compound. As with other designer drugs, motivation includes circumventing existing legal bans and standard methods of detection. Additionally, there is a desire to tailor-specific properties such as duration of effect and subjective experience. Another pressure motivating the emergence of novel illicit arylcyclohexylamine compounds has been the growing awareness of serious cystic and renal problems related to chronic ketamine use. Beginning as reports on drug user forums, long-time users have begun describing hematuria, urinary incontinence, urgency, and pain.[23] In 2007, the first clinical report confirmed severe lower urinary tract symptoms following chronic ketamine use. This case series described 10 patients exhibiting detrusor overactivity with overflow incontinence. One patient even required an augmentation enterocystoplasty where a segment of bowel was removed and sutured onto the bladder. In this patient, continued ketamine abuse resulted in acute renal failure.[23]

The year 2010 saw the emergence of methoxetamine, prominently marketed as a "bladder friendly" alternative to ketamine.[24]

ORIGINS OF METHOXETAMINE

The origins of specific designer drug compounds are often shrouded in mystery. Methoxetamine may be an exception. An interview in the February 2011 edition of Vice, an international arts and culture magazine, introduced "M.," an underground pharmaceutical scientist, who took ownership for the creation of methoxetamine.[25]

Only 13 years old, M. was badly injured in a London Irish Republican Army bombing resulting in the amputation of his left hand and chronic, agonizing phantom limb pain. In a quest for improved analgesia and "altered states," M. pursued a Master's degree in neuropsychopharmacology. Ultimately, he exited academia to strike out as an independent pharmaceutical researcher and entrepreneur. M. described being especially drawn to the arylcyclohexylamine class because of their dual properties as pain relievers and antidepressants.[25]

Feeling it his duty to personally test the chemicals he designed, M. described self-injecting 3-MeO-PCP, a compound closely related to methoxetamine. Found suicidal and catatonic, he was admitted for 3 weeks to an inpatient psychiatric ward. Upon discharge, he returned home to find the arylcyclohexylamine compounds he had been working on confiscated and his girlfriend gone, exasperated with his self-destructive ways. He noted that, in retrospect, his judgment had been clouded by near daily use of methoxetamine and related compounds: "I've come to realize that dissociatives have a really dark side to them that classic serotonergic psychodelics (like lysergic acid diethylamide [LSD]) don't." He added, "[t]he arylcyclohexylamines have a tremendous therapeutic potential, but they have a great abuse potential as well."[25]

PHARMACOLOGY

Methoxetamine is a member of the arylcyclohexylamine class.[26] This class acts on the glutamatergic system via antagonism of the *N*-methyl-D-aspartate (NMDA) receptor.[26] Although much is known concerning the pharmacology of this class of compounds, little is known specifically concerning methoxetamine.

Methoxetamine is a 3-methoxy, *N*-ethyl derivative of ketamine.[26,27] Drug user forums and the interview with M. provide some insights into why these structural changes were made. It has been suggested that the *N*-ethyl group was selected to increase the potency and duration of action relative to ketamine, while ameliorating the bladder toxicity associated with chronic use.[26] The replacement of the 2-chloro with the 3-methoxy group was to decrease the anesthetic and analgesic properties.[26] Importantly, these claims originate in the popular literature or online and are made without any supporting evidence. They should be considered speculative at best. It is worrying to see that they have worked their way into the (Fig. 1) peer-reviewed literature as statements of fact.[26]

Roth et al formally profiled methoxetamine and other ketamine and PCP analogs.[28] The compounds were screened at 57 molecular targets, including specific serotonin, dopamine, glutamate, γ-Aminobutyric acid, cannabinoid, opioid, sigma, and histamine receptors. Where significant binding

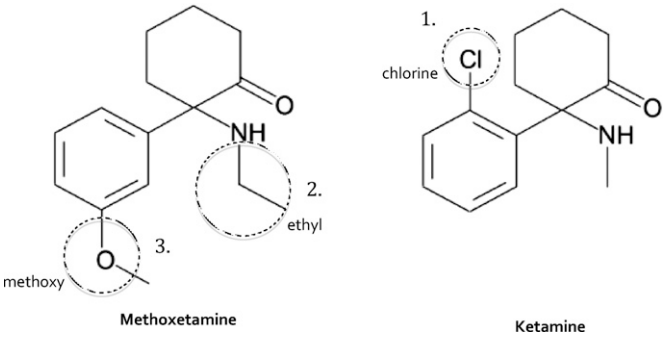

FIGURE 1. Note the close structural similarity between methoxetamine and ketamine. 1. The chlorine group is removed from ketamine. 2. The methyl on ketamine is replaced with an ethyl group. 3. The methoxy group is added to ketamine.

was observed, the binding affinity (pKi) was determined. Methoxetamine demonstrated affinity for the NMDA and serotonin receptors. Its affinity for the NMDA receptors was greater than that for ketamine, but less than for PCP (pKi of methoxetamine = 6.59, ketamine = 6.18, PCP = 7.23). For the serotonin receptor, methoxetamine demonstrated greater affinity than either PCP or ketamine (pKi of methoxetamine = 6.32, ketamine not reported, PCP = 5.65). Otherwise, methoxetamine did not demonstrate significant affinity for any other receptor classes.[28]

To investigate the claims of bladder safety, Wood et al administered methoxetamine to mice. They compared a daily dose of 30 mg/kg given over 3 months to a saline control. The mice who received saline demonstrated no renal or cystic changes, whereas the mice receiving methoxetamine had significant inflammation. Inferring from these findings, the authors conclude that "chronic use of methoxetamine in humans is likely to be associated with the same lower urinary tract symptoms that have been described for chronic ketamine use."[8]

EPIDEMIOLOGY

Prevalence data concerning methoxetamine use are extremely limited and comes principally from the United Kingdom. A novel attempt at elucidating methoxetamine use was made by Archer et al by analyzing samples from urinals in London.[29] Of the 12 urinals assessed in March 2012, methoxetamine was detected in only one. Wood et al surveyed patrons of "gay-friendly nightclubs" in South East London in July 2011. Of the 315 individuals surveyed, 1.6% reported using methoxetamine that day. Use that month was reported in 1.9% of respondents, and lifetime use was reported in 6.4%.[30] The Mixmag 2012 Global Drugs Survey, an online survey conducted by the British electronic dance music and clubbing magazine, reported that 4.9% of British respondents and 1.5% of American respondents endorsed methoxetamine use in the last 12 months. Of these, 73% reported taking methoxetamine because it was "easier to get ahold of" than ketamine, 20% felt it was "better value for money," and 18% "thought it was less damaging to liver/kidney."[31] The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), an agency of the European Union tasked with gathering and analyzing data of drug trends, reported that methoxetamine was the fourth most commonly offered legal high in European online shops in 2011 and 2012.[4]

In the absence of more rigorous prevalence data, we have elsewhere hypothesized that PCC contacts may provide a rough proxy for trends in legal high use.[32] In the United Kingdom, following the legislative ban on methoxetamine, PCC contacts concerning methoxetamine plummeted.[33] A similar trend was observed with views of TOXBASE, a Web site offered by the British National Poisons Information Service allowing registered health professional access to information on specific substances.[33] Admittedly, it is impossible to infer absolute population usage. Nevertheless, what is striking is the correlation of methoxetamine's ban with a decrease in PCC contacts, a pattern also observed with other designer drugs.[32]

CLINICAL PRESENTATION

Methoxetamine is an odorless white or off-white powder that is frequently sold in small, colorful packets.[27] It is sometimes marketed as "plant food" or "pond cleaner" and may include the "not for human consumption" or "warning: for research only" disclaimers commonly adorning the packaging of designer drugs.[7,34] Methoxetamine appears to be principally manufactured in China.[7] It is readily purchased online or in head shops.[7,27] It is sold in amounts ranging from 50 mg to 10 g, with smaller packets costing as little as $7 US.[5,27,35] Methoxetamine is referred to by a variety of names including "MXE," "m-ket," k-max," and "mexxy."[27] There have been recent reports in the popular media of the sale of methoxetamine online under the name "Roflcoptr."[36] However, the online drug user community holds the term in disdain. As one online commentator noted, "Of course, it's not really called Roflcoptr, any more than mephedrone was ever called 'meow meow' outside of the tabloids."[37]

Per user reports the most common route of administration is nasally, though methoxetamine is also ingested rectally, orally, and via intramuscular (IM) and intravascular injection.[5,7,27] Common reported dosages range from 10 to 100 mg.[5,27,35,38,39] Duration of effect following IM administration lasts less than an hour, whereas it can range 5 to 7 hours with oral consumption.[39] Of particular concern, depending on the route of administration, onset of effect is frequently delayed.[5,39] Following insufflation, users report a 30 to 90 minute delay before experiencing a response.[39] This may lead to repeated dosing and unintentional overdose. Tolerance and cravings have also been reported.[40]

Methoxetamine users report ketamine-like dissociative features including sensory deprivation, derealization, and dissociation from the physical body akin to a near-death experience.[27,38] Others report a pleasant intensification of

TABLE I. Summary of Reported Cases of Methoxetamine Toxicity

Age (in Years)	32-Year Old	19-Year Old	19-Year Old	17-Year Old	18-Year Old	42-Year Old
Sex	Male	Male	Male	Male	Male	Male
Country	USA	Switzerland	UK	UK	UK	UK
Route of Administration	IM	IV	Insufflation	Insufflation	Insufflation	Insufflation
Dosage	Unknown	Unknown	Unknown	Unknown	Unknown	500 mg
Analytical Confirmation	Not Confirmed	Confirmed	Confirmed	Confirmed	Confirmed	Confirmed
Coingestion	None	MDMA, Aripiprazole, Buproprion	Ketamine	None	None	5-APB or 6-APB, Alcohol
Past History	Hallucinogenic drug use	Drug Abuse, Psychosis, Depression, Attention Deficit Hyperactivity Disorder	Ketamine Use	None	Mephedrone Use	Unknown
Blood Pressure (in mmHg)	140/95	168/77	194/110	148/104	151/112	187/83
Heart Rate (in Beats per Minute)	105	134	107	72	67	135
Temperature (in Celsius)	37.2	37.6	36.7	34.5	36.7	38.2
Initial Presentation	Agitation, "Dissociative state"	Agitation, "Semistuporous," Ataxia	Drowsiness, Incoordination	"Drunk" and "Spaced out," Incoordination, LOC	"Suddenly felt very drunk," Incoordination	Found collapsed
Neurological Examination	Normal	Ataxia	Cerebellar ataxia, Dysarthria, Dysdiadochokinesis	Truncal ataxia, Dysarthria, Dysdiadochokinesis	Truncal ataxia, Dysarthria	
Eye Examination	Dilated Pupils Rotary Nystagmus	Dilated Pupils, Nystagmus	Dilated pupils, Nystagmus	Horizontal Nystagmus	Horizontal Nystagmus	Unknown
Psychiatric Examination	Agitation, Dissociation	Agitation		Dissociation		
Abnormal Laboratory Results		CK = 231	CK = 2,271, WBC = 19,800	CK = 118		
Time to Resolution of Symptoms	Complete: 8 Hours	Complete: 24 Hours	Vitals: 2–3 Hours, Cerebellar: 8–12 Hours, Complete: 4 Days	Vitals: 4 Hours, Complete: 16 Hours	Vitals: 3 Hours, Cerebellar: 16 Hours	Vitals: 2 Hours, Complete: 24 Hours
Treatment		Midazolam, Diazepam, Chlorprothixene		IV fluids, Passive Warming		Diazepam, Nasopharyngeal Airway
Author	Ward et al[5]	Hofer et al[37]	Shields et al[43]	Shields et al[43]	Shields et al[43]	Wood et al[42]

TABLE I. Continued

29-Year Old	28-Year Old	35-Year Old	30-Year Old	25-Year Old	26-Year Old	29-Year Old	Age Range: 17–42
Male	Male	Male	Male	Male	Male	Male	Male-All
UK	UK	UK	UK	Poland	Sweden	USA	UK-8 USA-2 Switzerland-1 Poland-1 Sweden-1
Oral	Insufflation	Insufflation	Unknown	IM	Unknown	Oral	Insufflation-6 IM-2 Oral-2 IV-1 Unknown-2
200 mg	Unknown	1,000 mg	Unknown	750 mg	Unknown	Unknown	Dosage range (in mg): 200–1000
Confirmed	Confirmed	Confirmed	Confirmed	Not Confirmed	Confirmed	Unknown	Confirmed-10 Not Confirmed-2 Unknown-1
Venlafaxine, Diphenhydramine	Unknown	Lithium	Alcohol	Codeine, Thyme Herb, Anise Oil, Potato Starch, Lactose Monohydrate, Powidon, Talc, Macrogol 600	Venlafaxine, 3 synthetic cannabinoids (AM-694, AM-2201, JWH-018)	None	Coingestion-8 (With Substances of Abuse-7) Only MXE-4 Unknown-1
PCP Abuse, Ketamine abuse	Unknown	Bipolar Disorder	Ketamine Use, Anabolic Steroid Abuse	8–10 Months of Daily Injections of MXE Alcohol Use, Codeine Abuse, Benzodiazepine Abuse, Barbiturates Abuse, Marijuana Abuse	Drug Abuse, Depression	Daily MXE Use	Prior Drug Use/Abuse-9 Past Psychiatric History-2
201/104	198/78	167/110	155/99	110–160/70–100		140/81	BP Range: 110–201/70–112
121	113	Within normal limits	80	68–140		117	HR Range: 67–135 HR > 100–8/13
Unknown	36.9	Within normal limits	37.9	37.0		37.1	Tmax: 38.2 Tmin: 34.5
Catatonic, Confusion, Tremor, Visual Hallucinations	Found collapsed, Agitation, Aggression, Drowsy	Found collapsed	Agitation, Confusion, Hallucinations	Initially Oriented But Somnolent, Became Agitated	Dead on Arrival (Autopsy Revealed Pulmonary Edema)	Agitation, Confusion	Altered Mental State-12 Agitation-6 Incoordination/Falling-4 Dead
Normal	Normal	Normal	Normal	Normal			Ataxia-4 Dysarthria-3 Dysdiadochokinesis-2
Dilated Pupils	Dilated Pupils	Dilated Pupils	Dilated Pupils	Unknown		Vertical nystagmus	Dilated Pupils-7/13 Nystagmus-6/13
Visual Hallucinations	Agitation	Delusions, "Ecstatic Behavior"	Agitation, Hallucinations CK = 5,023	Agitation		Agitation, Dissociation, Mood lability	Agitation-6 Dissociation-3 Hallucinations-2 Elevated CK-4/13 (Normal: 38–120) Elevated WBC-1/13
Complete: 24 Hours	Complete: 3 Hours	Complete: A Few Days	Complete: 24 Hours	Complete: 6–7 Hours		Complete: 24 Hours	Vitals: 2–4 Hours Cerebellar: 8–16 Hours Complete: 3 Hours–4 Days
Diazepam	Midazolam			Benzodiazepines, Physical Restraints		Diazepam	Benzodiazepines-6/13 Other-IV Fluids, Passive Warming, Nasopharyngeal Airway, Physical Restraints
Wood et al[42]	Wood et al[42]	Westwell et al[33]	Misselbrook and Hamilton[44]	Sein et al[45]	Wikström et al[51]	Wilde et al[6]	

sensory experiences.[27,38] Some describe vivid visual hallucinations such as "spinning sensations" and "naturalistic hallucinations in waves."[38,41] Coining the phrase "MXE vision," one user reported that his "field of vision was very bright and intense, the colors were vibrant and it was hard to focus on any one thing."[40] Others describe poignant recollection of past memories and dreams.[42] The overall experience has been characterized as "euphoric"and "full of empathy," whereas others emphasize its "more introspective" nature.[38,40]

Higher doses of methoxetamine result in a dissociative experience coined the "m-hole," a reference to ketamine's "k-hole."[28] With the m-hole users report a longer come up and duration of effect, but otherwise a similar subjective experience.[27] Although descriptions vary, the common feature is a profound derealization and depersonalization extending to loss of individual identity or the existence of the outside world. Vivid hallucinations and delusions are also commonly described.[27]

The m-hole can be distressing to some. One user wrote that his "[b]ody felt light but not comfortable. . .Thoughts were disintegrated, I lost sense of space[.]"[40] Another reported, "I was at first scared because of how strong and confusing it was. I was having very bizarre thoughts and thought those were real. I was in a bad trip for a second. But then I decided no way. I took control of the experience by becoming the primary conscious and feeding thoughts to myself like 'you are on drugs, just go with it because there is no turning back.' Then I got a grip and I could effectively enjoy the hole."[43]

Commonly reported untoward effects include dizziness, confusion, time distortion, aphasia, synesthesia, psychomotor agitation, and loss of consciousness.[5,27,38,39,41] Methoxetamine users also describe unpleasant symptoms including vertigo, incoordination, nausea, and vomiting, consistent with the cerebellar symptoms associated with toxicity described below.[5,27,38] One user reported, ". . .my balance was destroyed. Speech still slurred. A complete lack of understanding of words/numbers/equations etc. anything that was remotely lingual was virtually impossible to comprehend."[42]

Withdrawal symptoms following intoxication include low mood, cognitive impairment, and insomnia.[27,38]

There is a paucity of information describing the acute physical and psychological effects of methoxetamine use that may rise to clinical attention, and none concerning long-term effects. We identified 13 cases of methoxetamine toxicity in the literature, 2 from the United States and the rest from Europe (Table I).[5,7,8,35,39,44–47] All cases were males with ages ranging from 17 to 42 years old and a median age of 28. Initial presentation was generally because of some combination of loss of consciousness, in coordination with falls, agitation and aggression, and audiovisual hallucinations and delusions. During initial presentation, it was common for the mental status to fluctuate between comatose, confusion, and agitation and aggression.

The acute methoxetamine toxidrome can be roughly divided into three types of symptoms: dissociative/delirious, sympathomimetic, and cerebellar (Table II).

Dissociative symptoms associated with methoxetamine toxicity refer to a range of altered states of consciousness including catatonia, as well as psychotic symptoms including audiovisual hallucinations and delusions. However, only 5 of the 12 cases presenting alive described these features. Much more commonly, 11 of the 12 cases described states of waxing and waning consciousness that include confusion, agitation and aggression, more consistent with delirium.[7,8,35,39,44–47] We propose that this symptom group might best be described as dissociative/delirious. One case described a man found catatonic by his mother who presented confused and endorsing visual hallucinations.[44] Another patient described being "in contact with both heaven and hell and the spirit of his death father," though he denied frank hallucinations.[35] He presented as "ecstatic" and appeared confused as to the origins of nearby visual and auditory stimuli. Amnesia, perhaps related to delirium, is also described in two patients.[8,46] Upon presentation, one case was observed to exhibit retrograde amnesia in addition to "talking gibberish."[45] Another patient, brought to the emergency department after running into traffic and lying down on the street, exhibited "partial amnesia" as well as mood lability and confusion.[8]

The sympathomimetic symptoms of methoxetamine toxicity include tachycardia, hypertension, pyrexia, tachypnea, and agitation and aggression. Of the 12 cases presenting alive to the emergency department, 9 were tachycardic with a maximum heart rate of 140.[7,8,35,39,44–47] All cases were

TABLE II. Clinical Features of Methoxetamine Toxicity

Dissociative/Delirious
Depersonalization
Derealization
Catatonia
Audiovisual Hallucinations
Delusions
Confusion
Altered/Loss of Consciousness
Agitation
Aggression
Amnesia
Mood Lability
Sympathomimetic
Tachycardia
Hypertension
Pyrexia
Tachypnea
Pupillary Dilation
Cerebellar
Truncal Ataxia
Incoordination/falls
Dysarthria
Dysdiadochokinesis
Nystagmus (Horizontal, Vertical, and Rotary)

hypertensive with maximum systolic pressure of 201 mmHg and maximum diastolic pressure of 112 mmHg.[7,8,35,39,44–47] Body temperature instability was a less consistent finding with three cases of pyrexia and one of hypothermia (temperature of 94.1°F).[7,39,44,45] Respiratory rate was not reliably reported, being elevated in only one of the three cases with data.[8] Pupillary mydriasis was commonly observed.[7,35,39,44–46,48] Agitation and aggression was associated with initial presentation.[35,39,44,46] In most cases, autonomic symptoms resolved within 2 to 3 hours, with a maximum time to resolution of 8 hours.

Although the dissociative/delusional and sympathomimetic symptoms of methoxetamine toxicity are akin to those seen in ketamine toxicity, the cerebellar symptoms are distinct.[44] Five of the 12 patients presenting alive demonstrated cerebellar symptoms including truncal ataxia, incoordination, dysarthria, and dysdiadochokinesis.[39,44,48] Falling was commonly related to initial presentation. Horizontal, rotary, and vertical nystagmus were also frequently described.[7,8,39,44] Symptoms of cerebellar dysfunction were usually the last to remit, taking up to 4 days to completely resolve.

Among the cases described, the largest dose of methoxetamine consumed was by a 35-year-old male with a history of bipolar disorder.[35] He reported insufflating 1000 mg, approximately 10 to 20 times greater than the usual dose. There was no evidence of consumption of other substances. He was found unresponsive. Upon arrival to the emergency department, he had a Glasgow Coma Score of 14, blood pressure of 167/110, a normal heart rate, and his neurological examination was unremarkable save for pupillary mydriasis. The patient exhibited prominent delusions requiring psychiatric hospitalization, which resolved after several days.

The literature describes one death related to methoxetamine toxicity.[5] A 26-year-old male was found unconscious in his apartment with bags labeled "MXE" and "haze" beside him. No further history concerning clinical course was available. In addition to methoxetamine, the toxicology report revealed the presence of tetrahydrocannabinol (THC), three synthetic cannabinoids, and venlafaxine and its metabolite desmethylvenlafaxine. Cause of death was declared unknown, though autopsy revealed pulmonary edema.

As in the case above, methoxetamine is often consumed with a wide variety of other psychoactive substances. To enhance effect and duration, users report combining it with LSD, phenethylamines such as 2CC, tryptamines such as α-methyltryptamine, and amphetamine analogs such as MDAI, among other substances.[36] Of the 13 cases described in the literature, 6 also had ingested other substances of abuse including MDMA, 5-APB, 6-APB, alcohol, codeine, THC, and synthetic cannabinoids,[5,39,45–47] and presumably licit substances including aripiprazole, bupropion, chlorprothixene, and venlafaxine.[5,39,45] Nothing is known concerning the interaction of methoxetamine with other substances, though, online forums caution against combining it with alcohol, THC, SSRIs, or MAOIs.[38]

The case reports do not reveal consistent laboratory abnormalities. Elevated creatine kinase (CK) was observed in two patients with one demonstrating a maximum CK of 2,271 at 13 hours postintoxication.[39,43] Although this may be suggestive of rhabdomyolysis, also seen with PCP and ketamine intoxication, this patient also had extensive bruising making the cause of the elevated CK uncertain.[43] In addition, this patient had an elevated total white blood cell (WBC) count of 19,800 cells per μL with no evident cause identified.[43]

Methoxetamine is not identified in standard urine drugs screen though it can be detected with specialized testing such as gas chromatography–mass spectroscopy.[46] Overall, commonly available laboratory tests do not appear to aid the identification of methoxetamine toxicity.

MANAGEMENT OF ACUTE TOXICITY

At present, there are no specific management recommendations for acute methoxetamine toxicity.[41] In light of the similarities with PCP and ketamine both in terms of pharmacology and clinical presentation, it would be reasonable to treat methoxetamine toxicity similarly.[41,46] Agitation and aggression may be addressed with benzodiazepines.[41,46] Antiemetics can assist with nausea and vomiting.[41] Rhabdomyolysis can be prevented or managed with intravenous (IV) fluids.[41,46] Malignant hypertension can be addressed with benzodiazepines, sodium nitroprusside, or phentolamine, though beta-blockers should be avoided because of worsening hypertension caused by unopposed α-adrenergic stimulation.[46] Respiratory support should be provided as needed.[41,46]

Of the 13 cases described, 6 received benzodiazepines.[8,39,45,47] One was prescribed the typical antipsychotic chlorprothixene for insomnia.[39] One patient required a nasopharyngeal airway for respiratory support.[44] The remaining 6 patients received no pharmacological treatment.

It almost goes without saying that at this time there are no FDA approved indications for methoxetamine. That being said, two researchers in Italy have speculated that should methoxetamine share ketamine's antidepressant and antisuicidal properties it may have therapeutic potential.[26]

MILITARY CONSIDERATIONS

In recent years, designer drugs have emerged as a marked threat to the mission readiness in the U.S. military. "The U.S. military represents a microcosm of our much larger population and in many ways strives to be a reflection of the society we serve," stated Vice Admiral Nathan the Surgeon General of the U.S. Navy, "so we share many of the same health and safety issues as the general population, including the increased use of these dangerous and debilitating drugs - which not only affect our service members' health, but also our readiness as a military force."[2] U.S. military physicians have been on the forefront of describing the clinical presentations of spice and bath salt toxidromes in case reports and case series.[1,49] The 2011 Department of Defense Health Related Behaviors Survey, a large anonymous survey of

active duty personnel, reported that in 2011, 4.7% of respondents endorsed lifetime use of spice, with 1.3% using in the past 12 months and 0.2% in the past 30 days.[49]

Our goal in this article has been to describe a designer drug before it has gained prominence in the United States and the U.S. military.

For both spice and bath salts, clinical awareness within the military and the broader civilian medical community occurred only after a "critical mass" of patient presentations. Though there are clinical and popular reports of methoxetamine use in the general U.S. population, we are not aware of any clinical reports of methoxetamine use or toxicity within the U.S. military. However, that does not mean service members are not using this substance. On the drug forum Bluelight, a user named "idontdothizz" described celebrating with methoxetamine following a successful day at Military Entrance Processing Stations (MEPS) culminating with swearing in to the U.S. Navy. Initially struggling with a "bad trip," idontdothizz described in euphoric terms being back at the MEPS station: "I could fly around extremely fast through the whole building. I could fly everywhere and see everything vividly. This place was my play thing I could do anything I wanted and it was awesome.... I could not believe that I could do such a crazy thing."[43]

Our experience with spice and bath salts has taught us to look to Europe, particularly the United Kingdom, to anticipate the next substance to hit United States.[1,50,51] With both spice and bath salts, there was an approximately 2-year lag time.[1,50,51] Methoxetamine was first detected in England in late 2010.[5,41] Although population usage data are lacking, English PCC calls peaked in the spring of 2012.[6] Extrapolating from this admittedly inexact data, we would expect its presence in the United States to grow in early 2014.

Another lesson we have learned with spice and bath salt is that the initial wave of a small handful of compounds is quickly followed by a proliferation of dozens, if not hundreds of structural analogs.[1] True to form, there are already reports of multiple other ketamine and PCP analogs marketed as designer drugs.[34] In recent years, the EMCDDA has identified more than 40 new designer drugs in Europe annually. The United Nation Office on Drugs and Crime recently reported that the number of new designer drugs increased by "more than 50% in less than three years to 251 by mid-2012[.]"[3] This only heightens the urgency of anticipation and early detection of emerging designer drugs.

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