FACT SHEET

Methoxetamine

October 2013

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A. General information

Recent reported intoxication in Belgium

Date: 18/10/2013
Lab analysis date: 22/10/2013
Substance: methoxetamine
Product type: powder
Colour: white
Region: Antwerp

Uneventful recovery. No further details known.

Created
November 2010

Updated
October 2013

Type
Psychotropic substances

Group
Others

Name
Methoxetamine

Nature of substance
It is an arylcyclohexylamine, derivative of ketamine, where the 2-chloro group on the phenyl ring and the N-methyl group on the amine have been replaced by 3-methoxy and N-ethyl groups, respectively.

Systematic chemical name
2-(3-Methoxyphenyl)-2-(ethylamino)cyclohexanone

Physical description
White powder/crystals

B. Alerts

Alerts

One death in Sweden involving Methoxetamine, January 2012
On 4 June 2012 the NFO informed: January 2012. 27 yr old male from south of Sweden with abuse problems. Findings: 8.6 µg Methoxetamine / g postmortem femoral blood. Other findings were 0.001 µg THC /g postmortem femoral blood and spice-analogues AM694, AM2201 and JWH 018 (postmortem femoral blood). Apart
from this they also found 0,3 µg Venlafaxin and 0,4 µg O-desmetylvenlafaxin / g postmortem femoral blood.

**Acute intoxication case registered in Rome and related to the consumption of methoxetamine, February 2012**

On February 2012, a 27 years old male was admitted to an emergency department in Rome. At admission, the patient was tachycardic (HR 120 bpm), confused, hallucinated and severely agitated; diazepam was administered i.v. By October 2011, he was treated with valproic acid, risperidone and quetiapine for a psychosis. The day after admission, a treatment with midazolam 15 mg/day, delorazepam 7 mg/day and valproic acid 400 mg/day was started: subsequently, the delorazepam dosage was increased up to 20 mg/day and haloperidol was added. The patient referred the consumption by snorting of half of a package. The package was labelled as methoxetamine (2-(3-Methoxyphenyl)-2-(ethylamino)cyclohexanone) purchased on Internet. He also referred the oral assumption of an undefined amount of dextromethorphan (“Aricodil tosse”, dextromethorphan bromidrate). Toxicological analyses performed by the Laboratory of Toxicology, “San Matteo” Hospital of Pavia, by means of GC-MS and LC-MS/MS on urine and serum samples and on a residue of the product consumed by the patient, resulted positive for methoxetamine. Urine resulted positive also for methorphan. Methoxetamine analytical standard was not available. However, through the product consumed by the patient, it was possible to estimate a concentration of methoxetamine of 167 mcg/ml in urine and 0,2 mcg/ml in serum.

**Reports to EMCDDA**

Seizures of methoxetamine have been reported throughout Europe. The most important cases are described here.

**Italy:** On 21 June 2013 the Italian NFP reported 12 clinical cases. Toxicological analyses performed on biological samples (blood and/or urine) resulted positive for methoxetamine (analytically confirmed).

**Austria:** On 12 December 2012, the NFP reported a *fatal intoxication* involving methoxetamine. The substance was confirmed in biological samples analysed at the Department of Forensic Medicine, Medical University of Vienna in August 2012. 'Central circulatory failure due to a Methoxetamin overdose' was provided as the cause of death, however, no further details are available at present.

**United Kingdom:** In June 2012 the NFP informed that Methoxetamine was found in 6 fatal cases and 2 criminal cases during the period January-June 2012. Information from ROAR Forensics Ltd, Malvern.

**United Kingdom:** On 28 February 2012 the NFP sent this information that was kindly provided by Dr Alun Hutchings, Dr Andrew Westwell and Dr David Caldicott of the WEDINOS Group.

**France:** On 23 February 2012 the NFP reported a technical folder on MXE made by the French FP from national data and forum users analysis.
**United Kingdom:** On 22 February 2012 the NFP reported [updated information](http://www.buyresearchchemical.co.uk) related to methoxetamine.

**Belgium:** On 26 October 2011 the NFP informed that a Flemish hospital consulted the Belgian Poison Center after a patient complained about dizziness after taking methoxetamine. It was the patient himself who mentioned the substance, but no blood or urine sample were taken to confirm the presence of methoxetamine.

**United Kingdom:** On 9 November 2010, the UK NFP informed on the first collected sample of a packet labelled 'Methoxetamine', which contained 250 mg of high purity white powder. The product was bought on 30/09/2010 on the Internet (http://www.buyresearchchemical.co.uk).

### C. Pictures

Methoxetamine is sold and used as a white powder.

### D. Clinical information

**Usage**

Methoxetamine is used in the same way, and in the same settings as ketamine. It appeared on the market after the scheduling of ketamine, making this drug less accessible to users.

Methoxetamine is usually insufflated, although IM injections have been reported.

According to user reports, the psychoactive effects of methoxetamine are comparable to those of ketamine, although with a longer duration of action. These include euphoria, and feelings of severe dissociation (leading to uncoordinated behaviour, e.g. trouble standing up or walking) and change of time perception (time dilatation).

Like ketamine, higher dosages can lead to total dissociation (the so called “K-Hole”).

Lasting anti-depressant-like effects have been described by several users of the drug.

**Modes and scope of the established or expected use**

**Pharmacology:**

The mechanism of action is reported to involve NMDA receptor blockade and dopamine reuptake inhibition, although formal pharmacology has not been determined (Ward, 2011).

**Recreational dosage:** 20-100mg, insufflated.

**Health risks**

**Toxicity and adverse effects:**

*Wood et al* (2011) (United Kingdom) report a case series of three individuals with acute toxicity related to the analytically confirmed use of methoxetamine. The paper reports clinical features suggestive of a “dissociative/catatonic” state similar to that
seen with ketamine and clinical features of acute sympathomimetic toxicity with significant tachycardia and hypertension.

Hofer et al (2011) (Switzerland, Austria) report an analytically confirmed case of intravenous methoxetamine use. The observed symptoms were tachycardia, hypertension, confusion, agitation, stupor, ataxia, mydriasis, and nystagmus. The paper also suggests that the effects were consistent with ketamine-induced adverse effects and resolved with symptomatic treatment.

**Intoxication and treatment:**
Side effects include anxiety, blurred vision, impaired concentration, sympathomimetic effects (tachycardia), nausea, possibly panic attacks, insomnia. Loss of consciousness appears at very high dosages.

Intoxication can lead to neurological impairment and reversible cerebellar toxicity, which in most cases resolves spontaneously after 24 hours, but in some cases can last for several days. Treatment of overdosage is mainly supportive and symptomatic, no specific antidote is available.

It is unclear whether methoxetamine demonstrates the same bladder toxicity that has been reported after extensive use of ketamine.

**Other uses**
unknown

**E. Legal status**

Controlled substance in:
Austria, Denmark, Germany, Greece, Hungary, Italy, Portugal, Slovakia, Slovenia, Sweden, Turkey, United Kingdom, Republic Belarus, Japan.

**F. References**

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Methoxetamine Froum, Drum & Bassarena
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http://www.digitaljournal.com/article/318545

http://www.methoxetamine.co.uk
http://www.methoxetamine.co.uk
G. Chemistry

Systematic chemical name
2-(3-Methoxyphenyl)-2-(ethylamino)cyclohexanone

Other chemical names and variants

Chemical Abstracts Service (CAS) registry number
1239943-76-0

Physical description
White powder/crystals

Molecular information

Molecular structure:

Molecular formula: $\text{C}_{15}\text{H}_{21}\text{NO}_2$

Molecular weight: 247

Identification and analytical profile provided by LGC Forensics Ltd. and can be found at the end of this document.
GCMS and High Resolution LCMS and LCMS² Data

Methoxetamine

C₁₅H₂₁NO₂  Theoretical mass of [M+H]^+ = 248.1645

Full Scan Accurate Mass LCMS. Elemental confirmation
GCMS and High Resolution LCMS and LCMS$^2$ Data
Full Scan accurate mass LCMS (low and high source energies) and accurate mass MS$^2$ product ion scan

T:\Xcalibur...\24thJan\b\ACCN_26577  27/01/2011 03:38:31  492631-1BU

ACCN_26577 #531  RT: 3.16  AV: 1  NL: 1.32E9
F: FTMS + c ESI Full ms [50.00-650.00]

Full Scan no source energy

ACCN_26577 #529  RT: 3.14  AV: 1  NL: 8.47E7
F: FTMS + c ESI ad=100.00 Full ms [50.00-650.00]

Full Scan 100% source energy

ACCN_26577 #530  RT: 3.15  AV: 1  NL: 2.54E8
T: FTMS + c ESI d Full ms2 248.16@q35.00 [55.00-260.00]

Full Scan product ion MS$^2$
GCMS and High Resolution LCMS and LCMS² Data

EI-GCMS

ACGN26577-1321 RT: 9.55 AV: 1 NL: 2.30E5
F: v c EI Full ms

ACGN26577-1268 RT: 9.34 AV: 1 NL: 9.55E4
F: v c EI Full ms

TMS derivative

Generated by: Simon Hudson, HFL Sport Science Ltd

Page 3

February 4, 2011
Introduction

Ketamine (KET) is a phencyclidine (PCP) derivative that blocks noncompetitively the glutamate N-methyl-D-aspartate (NMDA) receptor; consequently, it inhibits the excitability of pain neurons to induce its dissociative anesthetic activity [1–3]. It binds as well but with a lower affinity to α and μ opioid receptors [1]. KET also inhibits nitric oxide synthase, hence further contributing to analgesia [1]. Furthermore, it acts as a noradrenergic and serotoninergic uptake inhibitor, both neurotransmitters being involved in descending antinociceptive pathways [4,5]. Because KET binds to both α(1) and α(2) receptors with μM affinities, this may suggest that α receptor-mediated neuronal remodeling may contribute to the antidepressant effects of KET [6]. Regarding MXE, its pharmacology and toxicology have yet to be elucidated. Although no formal studies have demonstrated the mechanism of action of MXE, it is likely to share the mechanism of action of KET through NMDA receptor antagonism and the inhibition of dopamine reuptake [7].

Dissociative activity of KET involves the sensory loss and analgesia as well as amnesia, which are not accompanied by actual loss of consciousness [8]. This unique experience could expand to the sense of a near-death experience (NDE) or even body splitting. For instance, Barbara Collier, an anesthetist, commented: “Ketamine allows some patients to reason that … the strange, unexpected intensity and unfamiliar dimension of their experience means they must have died” [9].

Ketamine causes mild stimulation of the cardiovascular (CVD) system without suppression of the respiration and gag reflex; thus, it has a good safety record [10]. It is used in the UK in both emergency departments (EDs) and chronic pain clinics for mild anesthesia in surgeries [11]. Furthermore, KET has been used as a therapeutic tool in a range of remaining conditions, including assisted psychotherapy for people with heroin dependence [12], alcoholism [13,14], resistant depression [15]. Furthermore, it has been reported that low-dose KET can also re-create a number of physiological abnormalities characteristic of schizophrenia [16,17]. However, administration of the drug in high doses for recreational purposes can cause CVD and respiratory toxicity. This makes its unregulated use outside the controlled environments a concern [18]. KET is an arylycyclohexylamine derivative with a molecular weight of 237.73 g/mol. Its chemical name is 2-(2-chlorophenyl)-2-(methylamino)cyclohexanone (Figure 1). KET has three modifications from the PCP main structure [19] (Figure 1). The first modification involves the replacement of the piperidene ring by a methylamine, which gives the same potency as PCP but increased tendency to induce nausea. The second modification involves the two chloro to the phenyl ring, which decreases the potency but increases the analgesic effect activity. The third substitution involves the addition of carbonyl group to...


From “Special K” to “Special M”  
O. Corazza et al.

Figure 1 Chemical structures of (A) PCP, (B) KET, and (C) MXE.

the cyclohexyl ring, which increases the elimination and decreases the duration of action of the anesthetic activity. KET has one chiral center at the C-2 carbon and thus has two enantiomers (R and S enantiomers). The S enantiomer has the more potent analgesic properties, whereas the postsynaptic properties and agitated behavior are more associated with R enantiomer [2,20].

Regarding pharmacokinetics, KET is extensively metabolized by N-demethylation producing norketamine, a noncompetitive NMDA receptor antagonist that might also exhibit enantioselective pharmacological activity, for example, (S)-norketamine has an 8-fold higher affinity than (R)-norketamine [21]. The pharmacokinetics of KET in analgesic doses after intravenous (IV), intramuscular (IM), and oral administration was investigated in healthy volunteers [22]. Plasma KET concentration–time curves were fitted by a two-compartment open model with a terminal half-life of 186 min. Absorption after IM injection was rapid and the bioavailability was 93%. However, only 17% of an oral dose was absorbed because of extensive first-pass metabolism. This high rate of first-pass metabolism may well explain why KET is typically not ingested. Similarly, MXE is generally taken by nasal insufflation (snorting), sublingual application, and IV and IM injection, with rectal use having been reported as well [7].

The objective of this paper is to comment on both the recreational use of KET along with its side effects and toxicity and one of its new derivatives, known as methoxetamine (MXE). The latter seems to be particularly popular compared with others such as N-ethylnorketamine, methoxyketamine, 3-MeO-PCP, or remaining derivatives, including tenocyclidine (TCP) and tiletamine (for a review of the gray literature) [23,24].

Materials and Methods

The literature search on the nonclinical/recreational use of KET and MXE was carried out in six databases: Ingenta, PubMed, Sciedirect, Scopus, Web of Knowledge, and Wiley (Table 1). Considering the limitations of peer-reviewed data in relation to latest trends of abuse and new psychoactive substances [11], such as MXE, the results were integrated with a qualitative assessment of a range of Web sites, drug fora, and other online resources including E-newsgroups, chat rooms, mailing lists, e-newsletters, and bulletin boards. The keywords used in this study included KET, ketamine, “Special K,” 2-(2-chlorophenyl)-2-(methylaminocyclohexanone, phencyclidine, PCP, MXE, “Special M,” 2-(3-methoxynonycyclohexanone, methoxetamine, MXE Powder, METH-O, “Special M,” psychedelics, near-death experience, NDE, recreational. The search was performed over a period of 10 months (January 2011–October 2011) in eight languages: English, Flemish, German, Hungarian, Polish, Italian, Norwegian, and Spanish. The inclusion criteria were any studies showing the chemistry, pharmacology, psychedelic and recreational use of KET and/or MXE. Nonrelevant studies were excluded. In this respect, the initial search retrieved 246 studies, of which 95 were excluded. The authors ended up with 151 studies being monitored on a regular basis and included 108 Web sites, 41 peer-reviewed data, one newsletter, and one monograph (see Figure 2). Data collected were kept confidential in a password-protected online database of the ReDNet (www.rednetproject.eu). Any personal data (that could be identifiable) collected from online fora were kept anonymous. The study was cleared for ethical approval by the School of Pharmacy Ethics Committee, Hatfield, Hertfordshire, UK (December 15, 2010, PHAEC/10-42).

Results

Nonclinical Use of KET

Nonclinical use of KET has increased exponentially since its first discovery as a safer anesthetic alternative to PCP [1,20]. It was discovered in 1962 by Calvin Stevens, a consultant for Parke-Davis/Warner [1,20]. In 1965, its first use as a recreational drug was recorded [20]. However, the recreational use became well known from the mid-1990s, when it was more popular than cocaine. This was partly because cocaine purity dropped and it was sold as a cheaper alternative [25]. KET, also known in these contexts as “Special K” or simply “K,” is widely used as a recreational drug in clubs, raves, and squat parties for self-experimental purposes, and it has caused problems as such in the EU and internationally. It might be difficult to understand why an anesthetic could become a popular substance of misuse. A few reasons can be identified [7,26]. These include its (1) short time-to-effect (30 second IV, 5–30 min intranasally, and 20 min orally) and duration of action, which can last up to three hours, (2) low cost, (3) peculiar psychoactive effects. The latter, known among users as the “K-hole” [27], range from confusional states, vivid dreams, hallucinations, flashbacks, referential thinking, dissociation, and depersonalization to...
psychotic experiences. It is known that at subanesthetic doses, KET intake has been anecdotally described to be associated with effects somewhat similar to those reported during a near-death experience (NDE) \[8,28–30\]. NDEs usually occur in various situations including cardiac arrest [31]; hypovolemic/septic/anaphylactic shock; intracerebral hemorrhage; cerebral infarction; near-drowning or asphyxia; apnea; electrostimulation of the temporal lobe [32]; and prolonged isolation/sensory deprivation [33]. Common features of the NDE include (1) the ineffable nature of the experience, (2) a sense of joy (cocaine-like rush), peace, and love, (3) the detachment from own physical body (out-of-the-body experiences) [34], (4) traveling along a region of darkness toward a light at the end, (5) visualization of past experiences, sometimes organized into a life-review [28,35], (6) visions and communications with deceased relatives and friends or “beings of light”, (7) a decision to return to life, and (8) altered perception of time, ataxia, among others [35].

Users reporting the near-death experiences felt out of the body or lost their senses and sometimes were feeling as out of the planet. One user, Mr. P, reported the above effects after he injected 100 mg of KET IM while he was listening to a piece of music. He said: “I gradually lost my senses. The music was very distorted. I tested myself by asking basic questions about mathematics, the names of those I love, etc., then suddenly I wasn’t interested in this anymore. So I tried to concentrate on ‘who I am’ and I lost the interest again. Visions become blurred. It wasn’t meaningful who I was any more, because I existed anyway. Then I tried the experience of death. I was going down a tunnel. I saw the planet Earth. I could feel the relationship between the human soul, Earth and the planets. I thought I was a doll, you know the matryoshka? I was the matryoshka of the entire system. I understood that earth is inside something else. I felt its gravity. All this is embraced within a system. I was nothing, but I knew that my place was on Earth” [30].

Another KET user reported: “Two years ago I was with my friends in Valencia. We went to the beach that day and we had some KET. We sat on the sand. The effects started very soon. I felt dizzy and I had to lie down. I closed my eyes. The first thing that I remember is that I felt somehow I was going very fast and that I left my body. It was not frightening. Subsequently, I saw a tunnel

Table 1 Comparison between KET and MXE chemistry and effects

<table>
<thead>
<tr>
<th>Criteria</th>
<th>KET</th>
<th>MXE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical name</td>
<td>2-(2-chlorophenyl)-2-(methylamino)cyclohexanone</td>
<td>2-(3-methoxyphenyl)-2-(amino)cyclohexanone</td>
</tr>
<tr>
<td>Chemical class</td>
<td>PCP derivative</td>
<td>PCP derivative</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>237.73 g/mol</td>
<td>283.79 g/mol</td>
</tr>
<tr>
<td>Pharmacological class</td>
<td>Dissociative anesthetic</td>
<td>Dissociative anesthetic</td>
</tr>
<tr>
<td>Receptors</td>
<td>NMDA, (\sigma), and (\mu)</td>
<td>NMDA, (\sigma), and (\mu)</td>
</tr>
<tr>
<td>Routes of administration</td>
<td>IV, IM, intranasal, and oral</td>
<td>Intranasal, oral, sublingual, rectal, IM, and very rarely IV</td>
</tr>
<tr>
<td>Dosage</td>
<td>10–250 mg</td>
<td>10–100 mg</td>
</tr>
<tr>
<td>Onset of action</td>
<td>30 second–30 min</td>
<td>30–90 min</td>
</tr>
<tr>
<td>Duration of action</td>
<td>3 h 0 min 0 second</td>
<td>5–7 h</td>
</tr>
<tr>
<td>Desired effects</td>
<td>Depersonalization and out-of-the-body experiences, including near-death experiences; stimulation</td>
<td>Euphoria, empathy, coziness, pleasant sensory experience, dissociation, derealization, vivid hallucinations, introspection, antidepressant, dissociation from body (“M-hole”)</td>
</tr>
<tr>
<td>Risk of re-dose</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Tolerance</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Dependence</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Known adverse effects</td>
<td>Confusion, vivid dreams, hallucination, flashbacks, referential thinking, panic attack, agitation, cardiovascular issues, depression, dissociation, apnea</td>
<td>Confusion, dizziness, time distortion, aphasia, synesthesia, cardiovascular issues, acute cerebellar toxicity, and psychomotor agitation</td>
</tr>
<tr>
<td>Bladder toxicity</td>
<td>Yes</td>
<td>Not confirmed</td>
</tr>
<tr>
<td>Cerebellar toxicity</td>
<td>Not reported</td>
<td>Anecdotally reported</td>
</tr>
</tbody>
</table>

Figure 2 Flow chart illustrating identification of the studies included over the time frame January 2011–October 2011.
and a tiny little light which grew bigger and bigger. I was approaching this light when I heard a voice telling me to go back. So I asked ‘Why? I don’t want to go back.’ I had no reply. A being of light appeared. He wanted to show me something. A big screen also appeared. I saw earth and the planets. I have heard them breathing. I touched the stars and talked to the Sun (God). I cannot remember what he said but it was amazing. I kept thinking that it was wonderful and amazing. And then, suddenly, I was lying back on the beach!”

Ketamine effects and NDEs might bear some level of resemblance at a neurobiological level as well. In fact, both KET and NDEs involve events at glutamate N-methyl-D-aspartate (NMDA) receptors [8,29,36]. However, it is still unclear whether reported psychoactive effects of KET may appropriately fit into typically described features of an NDE.

**Adverse Reactions Associated with KET Misuse**

Miss L., a 23-year-old who tried KET only once in her life at a disco club, observed: “I felt a bit paranoid, I was going to die. The first effects started very soon. I felt very confused and normal reality just disappeared. I was dizzy and unable to walk. I started bumping against walls. I wanted to go out from the room where I was, but it was very cold. I had no-one close to help me.” [30].

The risk of physical harm from accidents, such as blackouts and bad falls, is also very high [18]. There are also reports of people with chronic opiate problems using KET for its anesthetic and analgesic effects [37,38].

Ketamine may lead to dependence and tolerance can develop quickly; hence, a larger quantity is required to achieve the same effects [18]. This can lead users to take it in intense “binges.” An immediate risk of taking KET in recreational settings is accidents, such as bad falls. The disconnection from the body can be dangerous in almost any situation other than lying down in a safe environment. Other adverse effects can include panic attacks and depression, and when taken in large doses, it can exaggerate pre-existing mental health problems [19,30,39]. Stimulant-like weight loss and loss of appetite have also been reported after periods of heavy use. The risks of KET use are increased if it is used with depressant drugs, such as alcohol. It can suppress breathing and heart function in rare cases, although more commonly it stimulates these functions. It is more likely to suppress breathing (i.e., give rise to a period of apnea) if taken as a fast IV [18]. When used with stimulant drugs such as ecstasy (MDMA) or amphetamines, it can also cause high blood pressure [3]. A number of reports suggest that KET can be used as a “date rape drug” as high doses can cause amnesia for events that happened while under the influence of the drug [27]. Three days after the consumption of KET, impairments of working, episodic and semantic memory have been reported [40,41]. One research study has shown that semantic memory impairments associated with recreational KET use are reversible after people stop or substantially reduce its use. However, impairment to episodic and possibly attentional functioning is longer lasting [41–43]. A problem with these studies is that the authors rarely, if ever, provide urine or hair test results to prove that their subjects are not misusing with other drugs at the time of testing. Cannabis and alcohol are particularly likely culprits as many KET users smoke cannabis and drink alcohol daily [27]. Some users also experience mild forms of schizophrenic-like symptoms and perceptual distortions associated with the use of KET for a short period after they have stopped taking the drug [26]. Initially, following its anesthetic use, clinicians reported the occurrence of confusional states, vivid dreams, and hallucinations as well as flashbacks [44]. The risk of death has been commented in a few reports [18]. According to a report by the European Monitoring Centre for Drugs and Drug Addiction [37], some 12 persons have died as a result of KET use (seven in the United States and five in Europe) in the previous 10 years. Only three of these deaths were associated with the ingestion of KET on its own [37]. Conversely, Schifano et al. [18] focused on KET misuse mortality figures (UK; 1993–2006), extracted from various sources, and identified 23 victims (typically men, in the 25–44 age group) who self-administered themselves with a miscellany of psychoactive compounds (including KET) and alcohol. KET was detected in four cases on its own, and they suggested that high safe profile of KET should be questioned.

The bladder toxicity issues associated with KET cannot be disregarded. KET is linked to severe bladder problems including incontinence, painful bladder, bladder shrinkage, and damage to kidney and ureter obstruction, which may lead to bladder removal [45–47]. However, the mechanisms of how KET causes bladder toxicity are still somewhat unclear.

**MXE**

The recent emergence of new synthetic drugs [7,48] has also involved the “KET/PCP-like drugs” market. Since 2010, MXE has been advertised and sold online as a legal alternative to KET [7,49]. Indeed, MXE can be acquired legally without a veterinary license, which is the minimum requirement for the purchase of KET in various countries, including the United States. In the UK, it became the first drug to be banned by the Government under a temporary class drug order in April 2012. Chemical name of MXE is 2-(ethylamino)-2-(3-methoxyphenyl)cyclohexan-1-one (Figure 1). Its molecular weight is 283.79 g/mol. It is available as a white or off-white hygroscopic powder. It differs from PCP by two modifications [7,50]. The first involves the removal of the piperidine ring and replacement by an ethyl amino group, which gives more potency than PCP but increases the tendency to induce nausea. The second modification involves the 3-methoxy substitution on the phenyl ring, which increases the μ-opioid receptor affinity, while at the same time removing its mood-altering effects.

Methoxetamine is available online as “MXE powder” and “Special M” in the form of white powder. It is labeled as “Not For Human Consumption” to circumvent the regulations regarding recreational drugs [7]. Primary route of administration of MXE is intranasal, oral, sublingual, rectal, and IM [51,52]. In addition, very rare cases of IV administration have been reported and included an unconfirmed fatality following an IV injection of both 80–100 mg MXE and 400 mg of 5,6-methylene dioxy-2-aminoindo- dene (MDAI) [51,52].

Desired effects of MXE and dosages are influenced mainly by the modalities of intake. The dosages can range from 20 to 100 mg for oral administration and 10–50 mg for IM administration. Some users suggest the increase in the dosage gradually without.
exceeding 50 mg on the first occasion when administered orally [53]. The perceived effect could be delayed of some 30–90 min after insufflation [54]. This might be dangerous as it often causes the user to ingest another dose of the substance [51], thinking that the first dose was inadequate. Duration of action of MXE has been described as being in the range of 5–7 h [53]. However, when taken IM, the effect of MXE is faster than orally (within 5 min) [51] and its duration of action is shorter (about one hour).

**MXE Desired Effects and Adverse Reactions**

As reported by users, Effects of MXE are similar to those of KET, but with longer delay in onset (90 min) and longer duration (5–7 h) when administered orally [51,53]. MXE ingestion may be associated with NDE whose common features are sensory deprivation, derealization, and dissociation from the physical body [19,47,55].

Its reported desired effects include euphoria, empathy, "coziness," pleasant intensification of sensory experiences especially while listening to the music, mild to strong sense of dissociation from the physical body, distortion of the sense of reality, vivid hallucinations, introspection, and brief antidepressant effects [51,53,56,57]. Users’ reports described MXE experience as “music sounds great,” “trapped inside a glass chopping board,” “not for social situation,” “feeling like another inanimate object,” “…just seems so absurdly surreal and it makes no sense, but I’m quite happy just to stare at the TV screen, feeling all snuggly and warm.” Somebody described MXE as a “big Christmas cardigan,” whose intake was providing both “spinning sensations” and “naturalistic hallucinations in waves,” overall referring to the “M-hole,” as opposed to the KET “K-hole” [51]. This described the subjective state of dissociation from the body, which may mimic the out-of-the-body experiences or NDE [18,19]. Most users’ reports concluded that MXE is different from KET mainly because of “longer come up,” which might lead to a high risk of re-dose, and its longer-lasting effects. In summary, MXE seems to work as a short-acting mood enhancer with powerful (visual) hallucinogenetic and dissociative properties. However, it ingestion might be associated with several side effects such as dizziness, confusion, time distortion, aphasia, synesthesia, and psychomotor agitation [53,57].

Methoxetamine withdrawal symptoms may include low mood and/or depressive thoughts [53], decreased levels of cognitive impairment, insomnia [53], and potential suicidal attempts [51].

Methoxetamine is allegedly used in combination with a variety of other drugs to enhance or prolong its effects and duration of action. These include LSD, 2CC (4-chloro-2,5-dimethoxyphenethylamine), alpha-MT (alpha-methyltryptamine), MDAI [53]. However, Web fora users do not recommend its consumption with alcohol, tetrahydrocannabinol (THC), selective serotonin reuptake inhibitors (SSRIs), or monoamine oxidase inhibitors (MAOIs).

Some side effects of KET such as agitation and CVD issues (e.g., increased heart rate and blood pressure) may be associated with MXE ingestion. Others have included painful bladder, ureter obstruction, papillary necrosis, and hepatic dysfunction [27,47,58]. Regarding psychopathological disturbances of MXE, it may seem appropriate to conclude that they are similar to those of KET [59].

Although MXE has been named as the “bladder-friendly” alternative to “Special K,” work is still needed to confirm that MXE is bladder friendly [47,50]. Users, admitted to accident and emergency department after having ingested MXE, have experienced both KET-like dissociative/catatonic and sympathomimetic effects such as agitation, tachycardia, hypertension, hallucinations, confusion, stupor, mydriasis, and nystagmus [47,50]. MXE was detected in all the patients’ serum. Other patients had acute cerebellar toxicity after nasal insufflations of MXE [60]. The toxicity needed several days to recover and was characterized by severe ataxia, slurred speech, nystagmus, incoordination, and reduced consciousness.

User reports on forums confirm these effects. For instance, a chronic user, after 18 months of taking MXE, reported that the drug’s effects were dose dependent in most cases [61]. He specified his favorite route as sublingual compared to oral as the latter gives slower effect. In low doses (20–35 mg), MXE seemed more of a social drug as “It gave no hangover, lowered inhibitions enough that I could dance and not care if it was bad, and allowed me to feel inebriated enough that I didn’t feel like I was missing out on drinking.” However, at higher doses (>40 mg), the dissociative effects started appearing as the user reported: “I found MXE very confusing, numbed the body and yet was still quite suitable for a rave or part setting where socialization would not be required…I occasionally investigated high doses on my own, but did not find them particularly to my liking. I prefer to be functional as I never have much spare time, so the ‘M-hole’ was not great for me. I only investigated it once. Any time I took doses above 60 mg I found that I would awaken the next morning feeling ‘fuzz’…It is not necessarily an unpleasant feeling, but I certainly feel impaired and would not be comfortable driving a car while experiencing it. It is very hard sensation to describe, but I feel mentally dulled and my vision feels odd.”

Another user has experienced the dissociative effect after about one hour of taking 80 mg MXE sublingually with 15 mg of 1-(2,5-dimethoxy-4-ethylphenyl)-2-aminoethane (2C-E) intranasally [57]. The user reported: “I became unable to follow the movie I was watching while waiting for the chemicals to take effect…From this point on memory is spotty as my mind had de-constructed the concepts of time, order, and reality. Eyes are closed for the duration of the trip. Visuals were truly breathtaking, impossible to relate to my beloved trip report readers. I had the sensation that my body had descended several feet below the earth. I felt as though my mind had disconnected from the confines of its physical structure, projected astrally and was moving though time space at an incalculable speed…I believe I experienced ego death which was terrifying at first but afterward I felt ecstatic.”

**Discussion and Conclusions**

After 50 years of its discovery, KET, or “Special K,” has led to the emergence of methoxetamine, or “Special M,” and possibly other derivatives such as 3-MeO-PCP, PCE, 3-MeO-PCE, tiletamine, and 1-(1-(2-thienyl)-cyclohexyl)morpholine (TCM). Most of these new substances share a number of characteristics that may constitute a public health challenge: (1) they are not approved for human consumption, (2) their intake is possibly...
associated with a number of unknown side effects/adverse reactions, (3) very few related pharmacological/toxicological data are available in the peer-reviewed, scientific, literature, with the limited knowledge being mostly restricted to preclinical studies, (4) they are rapidly appearing in always more sophisticated forms and remain unregulated for a long period of time, (5) they are most often synthesized in underground laboratories simply modifying the molecular structure of remaining controlled drugs, hence raising further concerns in terms of the presence of contaminating agents, (6) they are largely available online and thus "just a click" away from our homes and potentially available to everyone [7]. In addition, the current legal status of most of its derivatives may arguably facilitate the increasing levels of popularity of the drug and might affect as well the users' perception of risks associated with its consumption. In fact, the idea that legality can equate with safety still remains well grounded among some recreational users [18,19]. This work has presented an overview of the first 50 years of KET’s history and provided an original reflection on its role in the future. A possible limitation of the present study could be given by the fact that only publicly available Web sites, fora, and similar sources were monitored. Conversely, to improve the coverage of the study, not only the web pages but also more private ways of communication (including newsgroups, chat rooms, mailing lists, e-newsletters, and bulletin boards) were here considered.

More studies need to be carried out on the issues here described, especially focusing on the clinical pharmacological and acute/chronic toxicity characteristics of the whole range of the PCP-like drugs.

Conflict of Interest

The authors declare no conflict of interest.

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The Characterization of 2-(3-Methoxyphenyl)-2-(ethylamino)cyclohexanone (Methoxetamine)

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ABSTRACT: The analysis, characterization, and synthesis of 2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone (commonly referred to as methoxetamine, “MXE,” or “3-Me-O-2-Oxo-PCE”) are discussed. Analytical data (nuclear magnetic resonance spectroscopy, mass spectrometry, and infrared spectroscopy) are presented and compared to the structurally similar drug ketamine.

KEYWORDS: 2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone, methoxetamine, MXE, 3-Me-O-2-Oxo-PCE, designer drug, synthesis, characterization, forensic chemistry.

The DEA Special Testing and Research Laboratory received a request to characterize an unknown compound in a suspected drug exhibit from another forensic drug laboratory. The exhibit consisted of approximately 200 milligrams of a white powder seized in the northeastern United States. The infrared spectrum of the exhibit was markedly similar to ketamine HCl. However, its mass spectrum differed from ketamine by +10 Daltons (apparent molecular weight of 247 vs. 237 for ketamine), including a base peak of +10 Daltons greater than that of ketamine. Additionally, the chlorine isotope pattern found in ketamine was not present. A mass spectral library search using the 2011 Wiley Designer Drug Library resulted in no matches. We suspected that the compound might be methoxetamine (based on the mass spectral data) and obtained 100 milligrams of sample for structural elucidation at our laboratory.

Methoxetamine or 2-(3-Methoxyphenyl)-2-(ethylamino)cyclohexanone (Figure 1), commonly referred to as “MXE” or “3-MeO-2-Oxo-PCE,” is a new compound for sale over the Internet. Methoxetamine was originally publicized through an interview with an “underground chemist” who envisioned its dissociative properties and proposed that it would be “a stress-free version of ketamine” [1]. Although not currently scheduled under the U.S. Controlled Substances Act, methoxetamine may be considered to be an analog of ketamine (Figure 2) [2]; replacing the ortho chlorine in ketamine with a methoxy, and replacing the N-methyl with an N-ethyl. Herein, we report the structural elucidation of methoxetamine through nuclear magnetic resonance spectroscopy, mass spectrometry, infrared spectroscopy, and subsequent independent synthesis. The analytical data are also compared to the structurally similar drug ketamine. Additionally, analytical profiles of methoxetamine’s synthetic intermediates and its major synthetic impurity are presented to assist forensic chemists who may encounter these substances in casework.

Experimental
Chemicals, Reagents, and Materials
All solvents were distilled-in-glass products of Burdick and Jackson Labs (Muskegon, MI). All other chemicals and NMR solvents were of reagent-grade quality and products of Aldrich Chemical (Milwaukee, WI). Ketamine HCl was obtained from the reference materials collection maintained at this laboratory.

Nuclear Magnetic Resonance Spectroscopy (NMR)
NMR spectra were obtained on an Agilent VNMR 600 MHz NMR using a 5 mm Protune broad band detection, variable temperature, pulse field gradient probe (Agilent, Palo Alto, CA). The HCl salts of the samples were initially dissolved in
deuterochloroform (CDCl_3) containing 0.03% v/v tetramethylsilane (TMS) as the 0 ppm reference compound, and later base extracted using saturated sodium bicarbonate in D_2O. The sample temperature was maintained at 26°C. Standard Agilent pulse sequences were used to collect the following spectra: proton, carbon (proton decoupled), and gradient versions of the 2-dimensional experiments COSY, HSQC, and HMBC. Data processing and structure elucidation were performed using Structure Elucidator software from Applied Chemistry Development (ACD/Labs, Toronto, Canada).

Gas Chromatography/Mass Spectrometry (GC/MS)

Mass spectra were obtained on an Agilent Model 5975C quadrupole mass-selective detector (MSD) that was interfaced with an Agilent Model 7890A gas chromatograph. The MSD was operated in the electron ionization (EI) mode with an ionization potential of 70 eV, a scan range of 34-600 amu, and a scan rate of 2.59 scans/s. The GC was fitted with a 30 m x 0.25 mm ID fused-silica capillary column coated with 0.25 µm 100% dimethylpolysiloxane, DB-1 (J & W Scientific, Rancho Cordova, CA). The oven temperature was programmed as follows: Initial temperature, 100°C; initial hold, 0.0 min; program rate, 6°C/min; final temperature, 300°C; final hold, 5.67 min. The injector was operated in the split mode (21.5:1). Infrared spectra were obtained on a Thermo-Nicolet Nexus 670 FTIR equipped with a single bounce attenuated total reflectance (ATR) accessory. Instrument parameters were: Resolution = 4 cm\(^{-1}\); gain = 8; optical velocity = 0.4747; aperture = 150; and scans/sample = 16.

Synthesis of Methoxetamine

In accordance with Journal policy, exact experimental details are not provided. A procedure analogous to that of ketamine was utilized (Figure 3) for the preparation of methoxetamine and its intermediates [3].

Results and Discussion

NMR Elucidation

Proton and carbon NMR spectra as well as the assignments for methoxetamine HCl and ketamine HCl are presented in Figures 4-7. Assignments were based on proton chemical shifts and peak patterns, carbon chemical shifts, HSQC (1 bond carbon to proton correlations), HMBC (2-4 bond carbon to proton correlations), and COSY (2-3 bond proton-proton correlations) spectra. Assignments were further confirmed using ACD Structure Elucidator software.

The methoxetamine spectra (carbon and HSQC) contain 15 carbons: 1 ketone, 6 benzene (4 protonated), 1 aliphatic quaternary, 5 methylenes, and 2 methyis. The aromatic proton peak pattern for methoxetamine base clearly shows a 1,3-disubstituted benzene pattern: a triplet (7.29 ppm), a doublet (6.82 ppm), a doublet of doublets (6.82 ppm), and 1 small coupling doublet (6.75 ppm). In addition, the proton, carbon, and COSY spectra indicate the presence of an N\(\text{CH}_2\)\(\text{CH}_2\) whose methylene protons are not equivalent, the presence of a methoxy singlet at 3.8-3.9 ppm, and 4 methylenes bonded to each other in an n-butyl chain (as indicated by the multiple couplings to each proton and the COSY correlations). HMBC correlations show that the butyl chain is bonded to or very nearby the ketone carbon and the quaternary aliphatic carbon. The HMBC also indicates that the N-ethyl group, the n-butyl group and the benzene ring are bonded to or very nearby the quaternary carbon. Based on the molecular weight of 247 and the NMR data, the molecular formula is C\(_{13}\)H\(_{21}\)NO\(_2\). This formula indicates that there are 6 unsaturations and/or rings in the molecule: the benzene ring accounts for 4 and the ketone for 1, thus leaving 1 additional ring (no other unsaturations noted in spectra). The main NMR fragments are a benzene ring (with a methoxy at C3), a ketone, an N-ethyl, a quaternary carbon, and an n-butyl chain. The quaternary carbon chemical shift (69.7 ppm base) indicates it is bonded to one or more strong electron withdrawing groups. The structure of methoxetamine satisfies all this and also gives the lowest derivations of carbon chemical shifts (i.e., experimental versus calculated).

In contrast to methoxetamine, the ketamine base proton spectrum (Figure 7) displays two “doublet of doublets” (7.38 and 7.55 ppm) and two “triplet of doublets” (7.25 and 7.32 ppm) in the aromatic region, and a singlet at 2.10 ppm for the N-methyl group. The proton and carbon spectra of ketamine and methoxetamine are very different and are easily distinguished.

Mass Spectral Elucidation

The mass spectra of methoxetamine and ketamine are shown in Figure 8. The appearance of the mass spectrum of methoxetamine is similar to that of ketamine, at least at the higher mass range. The major dissimilarities between the two spectra are a difference of +10 Daltons for the peaks of methoxetamine versus the corresponding peaks of ketamine (base peak of m/z 190 versus m/z 180; peak at m/z 204 versus m/z 194; and peak at m/z 219 versus m/z 209).

The proposed fragmentation of methoxetamine is shown in Figure 9. Due to the similarity of the structures, the major fragmentation mechanisms of methoxetamine are expected to be similar to that proposed for ketamine [4]. Initial ionization occurs at the amine nitrogen which is followed by alpha cleavage to give structure A. Structure A can undergo neutral loss of CO to yield ion B, m/z 219. The newly formed radical site in structure B can undergo secondary alpha cleavages. Loss of a hydrogen radical from structure B (pathway a) results in structure C, m/z 218. Loss of neutral ethylene from structure B (pathway b) gives structure D, m/z 191 which likewise can lose a hydrogen radical to give structure E, m/z 190.

Structure B can also undergo ring closure (pathway c) to yield a radical cation (structure F) similar in stability to the parent ion. This ion can undergo further alpha cleavages to yield ions G, m/z 204 (loss of a methyl radical) and H, m/z 112 (loss of a methoxyphenyl radical).

FTIR

The FTIR spectra for methoxetamine HCl and ketamine HCl are illustrated in Figure 10. Comparison reveals somewhat similar absorption patterns, with the most prominent differences being in the region of 500-1600 cm\(^{-1}\). An absorbance found at 1725 cm\(^{-1}\) (due to a carbonyl stretching vibration) strongly indicates a carbonyl in the suspected methoxetamine (carbonyl
Figure 3 - Synthetic route for methoxetamine.

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Figure 4 - $^1$H and $^{13}$C NMR data for methoxetamine HCl.
Figure 5 - $^1$H and $^{13}$C NMR data for methoxetamine base.

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Figure 6 - $^1$H and $^{13}$C NMR data for ketamine HCl.
Figure 7 - $^1$H and $^{13}$C NMR data for ketamine base.

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Figure 8 - Mass spectra of (a) methoxetamine HCl and (b) ketamine HCl.
Figure 9 - Proposed fragmentation pathways for methoxetamine.
Figure 10 - FTIR spectra of (a) methoxetamine HCl and (b) ketamine HCl.
Figure 11 - Mass spectra of (a) 3-methoxyphenyl cyclopentyl ketone, (b) \textit{alpha}-bromo-(3-methoxyphenyl)-cyclopentyl ketone, and (c) 1-[(ethylimino)(3-methoxyphenyl)methyl]cyclopentanol.
Figure 12 - Infrared spectrum (a) and mass spectrum (b) of [1-(ethylamino)cyclopentyl](3-methoxyphenyl)methanone; methoxetamine synthesis impurity.
Figure 13 - $^1$H and $^{13}$C NMR data for [1-(ethylamino)cyclopentyl](3-methoxyphenyl)methanone HCl.

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Figure 14 - $^1$H and $^{13}$C NMR data for [1-(ethylamino)cyclopentyl](3-methoxyphenyl)methanone base.
stretch for ketamine is found at 1719 cm\(^{-1}\)). When methoxetamine HCl is compared to ketamine HCl, significant differences can differentiate the compounds, especially the absorbances at 1550-1600 cm\(^{-1}\) due to C-C stretching [5].

**Synthesis**

Methoxetamine was synthesized utilizing an analogous procedure for that of ketamine (Figure 3). A cyclopentyl Grignard was reacted with 3-methoxybenzonitrile to form 3-methoxyphenyl cyclopentyl ketone, which was then brominated \(\alpha\) to the ketone. The \(\alpha\)-bromo ketone was converted to the Schiff’s base with ethyl amine, which was then heated to form methoxetamine. The NMR, FTIR, and mass spectrum of the synthesized methoxetamine were in all respects identical to the unknown compound’s spectra. Mass spectra for the three intermediates are illustrated in Figure 11. GC retention time data for the respective compounds are presented in Table 1.

A significant amount of a by-product (impurity) was produced during the synthesis of methoxetamine. The FTIR (Figure 12a) of the synthesis impurity indicated that a carbonyl was present and its mass spectrum (Figure 12b) indicated a molecular weight of 247. The impurity was easily isolated from methoxetamine HCl by its solubility in acetone. The NMR spectrum (Figures 13 and 14) illustrated that this compound, like methoxetamine, contained a 1,3-disubstituted benzene (with a methoxy group at C3), an N-ethyl group, a ketone, a quaternary carbon, and an \(n\)-butyl chain. However, the proton and carbon chemical shifts and the HMBC correlations show that the ketone is the bridge between the benzene ring and a cyclopentyl ring and this cyclopentyl ring contains the quaternary carbon which is bonded to the N-ethyl group. The isolated impurity was characterized as [1-(ethylamino)cyclopentyl](3-methoxyphenyl)methanone (Figure 15).

**References**