Methoxetamine – a novel recreational drug with potent hallucinogenic properties

Jolanta B. Zawilska

Highlights
- Methoxetamine (MXE), a structural analogue of ketamine, is a novel designer drug.
- MXE is recreationally used due to its potent hallucinogenic and dissociative effects.
- Consumption of MXE bears a significant health risk.
- Long-term effects and interaction of MXE with other drugs of abuse remain to be elucidated.

Abstract
Methoxetamine is one of the constantly growing group of novel psychoactive substances that has emerged in recent years. The compound belongs to the arylcyclohexylamine class, which is used for its recreational and psychedelic effects. Methoxetamine is a structural analogue of ketamine, with a much longer duration of action and intensity of effects, and has been extensively advertised as its ‘legal’ and ‘bladder friendly’ alternative. This review surveys the current state of knowledge regarding the metabolism, pharmacology, prevalence and pattern of methoxetamine use, and analytical methods of its detection. Consumption of methoxetamine bears a significant health risk and may even lead to fatal intoxication. A significant amount of research is still needed in order to fully quantify the short- and long-term effects of methoxetamine and its interaction with other drugs of abuse.

Keywords
Methoxetamine; Novel psychoactive substances; Hallucinogenic/dissociative drugs; Toxidrome

1. Introduction
Recently, a new class of psychoactive substances, known as 'legal highs', 'herbal highs', 'designer drugs' or 'research chemicals', has emerged on the drug use market. They include a wide range of products, from natural plant-originated substances to semisynthetic and synthetic compounds (EMCDDA, 2013a, Johnson et al., 2013, Papaseit et al., 2014 and Zawilska, 2011). Based on the spectrum of exerted psychoactive effects, these compounds can be classified into four basic categories: synthetic cannabinoids ("Spice"/K2), stimulants, hallucinogens, and opioid-like drugs (Zawilska, 2011). The EU warning system operated by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) reported the appearance of 317 new psychoactive substances between 2005 and 2013 (EMCDDA, 2013a and EMCDDA, 2014). Importantly, the EU drug market report emphasizes that "while the appearance of new drugs is not a new phenomenon, over the last few years there has been an unprecedented growth in their number, type, and availability" (EMCDDA, 2013a).

Ketamine is a well-known anesthetic with a good safety profile, which is used particularly in pediatric and veterinary anesthesia, and as a co-analgetic in pain management. However, since the mid-1990s, its potent hallucinogenic and dissociative effects have afforded ketamine the status of a recreational drug used mainly by teenagers and young adults at dance clubs, raves, and squat parties (Morris and Walach, 2014). Common
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In May 2010, the first public report on effects of methoxetamine (2-(3-methoxyphenyl)-2-(ethylamino)cyclohexan-1-one; MXE or 3-MeO-2-OxoPCE), a new designer drug, was published on the Internet (Morris and Walach, 2014). An evolution of methoxetamine at the research chemicals and recreational drug market has been described by Morris and Walach (2014) in a comprehensive and elegant review on dissociative drugs. The drug is a member of the arylcyclohexylamine family; more specifically, it is a structural analogue of ketamine, where the 2-chloro group on the phenyl ring and the N-methylamino group of ketamine have been replaced by a 3-methoxy and N-ethylamino group, respectively (Fig. 1). Soon after, methoxetamine was extensively advertised as a ‘legal’ and ‘bladder friendly’ alternative to ketamine (EMCDDA, 2013b and Kjellgren and Jonsson, 2013). Methoxetamine is typically sold as a free base and hydrochloride salt in powder. The common street names of methoxetamine are: ‘MXE’, ‘Mexxy’, ‘M-ket’, ‘MEX’, ‘Kmax’, ‘Special M’, ‘MA’, ‘legal ketamine’, ‘Minx’, ‘Jipper’, and ‘Roflcoal’ (EMCDDA, 2013b).

By 2013, methoxetamine had been seized in a number of countries throughout Europe, including Belgium, Italy, Sweden, and the United Kingdom (EMCDDA, 2013b). Although in vast majority of samples, methoxetamine was the only detected compound; some of them also contained other psychoactive compounds, such as phenethylamines (e.g., 4-fluoroamphetamine), synthetic cathinones (e.g., methylone, mephedrone, and 3,4-methylenedioxypyrovalerone), synthetic cannabimimetics (AM-2201, JWH-018), benzodiazepines, methylphenidate, ketamine, amphetamine, methamphetamine, 3,4-methylenedioxy-N-methamphetamine (MDMA), cannabis, morphine, and heroin (EMCDDA, 2013b). Methoxetamine has been found in 18 out of 173 samples of controlled drugs submitted to the Spanish Drug Checking Service between 2009 and 2012: in 15 ketamine samples, and in single samples of MDMA, amphetamine and cocaine (Giné et al., 2014). In 2013, methoxetamine was brought under permanent control in the United Kingdom as a Class B drug (Home Office, 2013).

2. Metabolism and pharmacological properties of methoxetamine

In vitro studies using human liver microsomes and human liver S9 fraction revealed that methoxetamine undergoes a complex phase I metabolism, including N-deethylation, O-demethylation, hydroxylation, reduction, and dehydrogenation (Menzies et al., 2013). Kinetic studies with human hepatic CYP isoenzymes have demonstrated that N-deethylation is catalyzed by CYP2B6 and CYP3A4, O-demethylation by CYP2B6 and CYP2C19, and hydroxylation by CYP2B6 (Meyer et al., 2012). Using liquid chromatography–high resolution mass spectrometry (LC–MS)n, several different metabolites of the drug were identified, namely N-desethylmethoxetamine (normethoxetamine; a major metabolite), O-desmethyl-methoxetamine, O-desmethylnormethoxetamine, dihydrodromethoxetamine, O-desmethylhydroxynormethoxetamine, and hydroxynormethoxetamine (Fig. 2). Phase II metabolites were mainly mono-glucuronide conjugates (Menzies et al., 2013 and Meyer et al., 2012). An analysis of urine samples collected from three individuals presenting acute methoxetamine toxicity demonstrated the presence of in vitro microsomal metabolites, with the exception of O-desmethylhydroxynormethoxetamine (Menzies et al., 2013). Similar results were obtained by Meyer et al. (2012) for rat and human urine.
Confirmation of the important role played by CYP2B6 in methoxetamine metabolism is of clinical importance. As CYP2B6 is involved in metabolism of numerous drugs and xenobiotics, pharmacokinetic interactions between methoxetamine and other compounds are likely to occur. Furthermore, the rate of methoxetamine metabolism and its toxicity may depend on genetic polymorphism of CYP2B6. However, the precise nature of the biological activity of specific methoxetamine metabolites, if any, remains unknown.

Little is known about pharmacological activity of methoxetamine. Very recently, Roth et al. (2013) performed an in vitro examination of the neuropharmacological profile of methoxetamine by screening its activity at 57 molecular targets relevant to the action of the drug with the CNS. They found that methoxetamine has a sub-micromolar affinity for the glutamate N-methyl-D-aspartate (NMDA) receptor ($pK_i = 6.59$), which is comparable to that of ketamine ($pK_i = 6.18$), and binds to the phencyclidine site on the NMDA receptor. In addition, methoxetamine was found to exhibit a sub-micromolar affinity ($pK_i = 6.32$) for the serotonin transporter, thus resembling the property of phencyclidine ($pK_i = 5.65$). Furthermore, it has been shown that methoxetamine increases electrically-stimulated release of dopamine from slices of rat nucleus accumbens and inhibits the re-uptake of the amine (Davidson et al., 2014).

3. Prevalence and pattern of use

Currently, limited information is available regarding the prevalence and pattern of methoxetamine use, and existing studies should be taken with caution as many of them are based on online surveys and self-reports on user websites. Wood et al. (2012b) surveyed individuals attending gay-friendly nightclubs in south-east London in July 2011 on their use of novel psychoactive substances, cocaine, and MDMA. It was found that 206 out of 313 (65.8%) individuals reported having previously used a ‘legal high’. Of these, 6.4% reported lifetime use of methoxetamine, 1.9% reported its use in the last month, and 1.6% reported use on the night of the survey or planned to use it later that night. The results of the online 2012 Global Drug Survey conducted in November 2011 show that out of 7700 respondents from the United Kingdom, 4.2% and 2.4% reported using methoxetamine in the last year and previous month, respectively (EMCDDA, 2013b).

The most common routes of administration for methoxetamine include nasal insufflation ('sniffing' or 'snorting') and oral consumption, where it is swallowed either as a powder wrapped in a cigarette paper (so-called 'bombing') or dissolved in a solution. There are also reports on intramuscular/intravenous injections, sublingual, and rectal administration (Corazza et al., 2012, Kjellgren and Jonsson, 2013 and Östberg et al., 2013). Kjellgren and Jonsson (2013) analyzed 33 self-reported experiences of methoxetamine use from user websites, where methoxetamine was the only drug reported to have been used at the time, and found the total amount of methoxetamine taken during the experiences ranged from 10 to 200 mg. A common dose of methoxetamine reported by the users was 20–60 mg for insufflation, 40–60 mg for oral administration, and 15–30 mg for intramuscular injection. The duration of the drug's action depends on the route of
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4/20


Drugs found in
Agitation, aggression, confusion, tremor, visual hallucinations, delusions.
Oral
Drowsiness, tachycardia (heart rate 113 bpm), hypertension.
Nasal
Way of MXE administration
Nasal insufflation
Tachycardia, hypertension, cardiac and respiratory depression, and chest pain. A very recent study of an analytically-confirmed case of acute intoxication after inhalation of methoxetamine presented epileptic seizures, sinus bradycardia (48 bpm), elevation of the ST-segment in the electrocardiogram recording and hyponatremia (Imbert et al., 2014).

5. Methoxetamine-induced toxicity

Although methoxetamine is advertised as a bladder-friendly analogue of ketamine (e.g., Morris and Walach, 2014), results from recent studies performed on animals indicate that this may not be true. Daily treatment of mice with 30 mg/kg of methoxetamine for 3 months resulted in significant bladder inflammation with subsequent fibrosis and renal toxicity (Dargan et al., 2014).

A total of 110 non-fatal intoxications with methoxetamine have been reported by EMCDDA by the end of 2012, almost half of them being analytically confirmed: 1 in Belgium, 3 in France, 12 in Italy, and 36 in Sweden (EMCDDA, 2013b). There are a few published cases of methoxetamine toxicity (Abe et al., 2013, Hofer et al., 2012, Hydzik et al., 2013, Lukasik-Glebocka et al., 2013, Sein et al., 2012, Shields et al., 2012, Wikström et al., 2013 and Wood et al., 2012a; see also Loeffler and Craig, 2013), summarized in Table 1. In addition, Hill et al. (2013) characterized enquires regarding toxic effects of methoxetamine reported to the National Poison Information Service in the United Kingdom. The clinical features of methoxetamine-induced toxicity could be divided into the following main groups: (1) psychiatric – anxiety, hallucinations, panic, profound agitation, aggression, violence; (2) cognitive – black-outs, confusion, disorientation, amnesia, and lowered consciousness; (3) neurological – catatonic state, cerebral ataxia, mydriasis, slurred speech, drowsiness, tremor, vertigo, insomnia, and motor incoordination; (4) cardiovascular – tachycardia, hypertension, cardiac and respiratory depression, and chest pain. A very recent study of an analytically-confirmed case of acute intoxication after inhalation of methoxetamine presented epileptic seizures, sinus bradycardia (48 bpm), elevation of the ST-segment in the electrocardiogram recording and hyponatremia (Imbert et al., 2014).

### Table 1.

<table>
<thead>
<tr>
<th>Gender, age</th>
<th>Symptoms</th>
<th>Drugs found in biological samples</th>
<th>Treatment</th>
<th>Way of MXE administration</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute intoxication</td>
<td>Drowsiness, tachycardia (heart rate 135 bpm), hypertension (blood pressure 187/83 mm Hg), pyrexia (38.2 °C)</td>
<td>Serum: methoxetamine 0.12 g/mL, 5-APB or 6-APB</td>
<td>Diazepam</td>
<td>Nasal insufflation</td>
<td>Wood et al. (2012a)</td>
</tr>
<tr>
<td>M/42</td>
<td>Tremor, visual hallucinations, confusion, tachycardia (heart rate 121 bpm), hypertension (blood pressure 201/104 mm Hg)</td>
<td>Serum: methoxetamine 0.09 mg/mL, diphenhydramine and venlafaxine</td>
<td>Diazepam</td>
<td>Oral</td>
<td></td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Case</th>
<th>Symptoms</th>
<th>Methoxetamine Levels</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>M/24</td>
<td>Drowsiness, dysphoria, hallucinations, impaired motor coordination, blood pressure up to 140/90 mm Hg, heart rate up to 120 bpm</td>
<td>Methoxetamine: serum 450 ng/mL, urine 7200 ng/mL</td>
<td>Nasal insufflation</td>
</tr>
<tr>
<td>M/28</td>
<td>Extreme agitation, aggression, confusion, hallucinations, tachycardia (heart rate 105 bpm)</td>
<td>Methoxetamine: serum 270 ng/mL, urine 660 ng/mL</td>
<td>Benzodiazepines</td>
</tr>
<tr>
<td>M/25</td>
<td>Lost of consciousness, heart rate 68–140 bpm, blood pressure 110–160/70–100 mm Hg, profound agitation</td>
<td>Benzodiazepines</td>
<td>Intramuscular injection</td>
</tr>
<tr>
<td>M/27</td>
<td>Lost of consciousness, incoherent and slurred speech</td>
<td>Blood: methoxetamine 0.21 μg/g AM-2201 0.001 μg/g</td>
<td></td>
</tr>
<tr>
<td>M/19</td>
<td>Severe cerebellar ataxia, drowsiness, slurred speech, dilated pupils, nystagmus, incoordination, reduced conscious level, tachycardia (heart rate 107 bpm), hypertension (blood pressure 194/110 mm Hg), increased serum creatine kinase (701 U/L)</td>
<td>Serum: methoxetamine 0.24 mg/L</td>
<td>Nasal insufflation</td>
</tr>
<tr>
<td>M/17</td>
<td>Severe cerebellar ataxia, slurred speech, reduced conscious level, imbalance, incoordination, horizontal nystagmus, hypothermia (34.5 °C), hypertension (blood pressure 148/104 mm Hg)</td>
<td>Serum: methoxetamine 0.45 mg/L</td>
<td>Intravenous hydration, warming</td>
</tr>
<tr>
<td>M/18</td>
<td>Truncal ataxia, slurred speech, incoordination, imbalance, reduced conscious level, minor horizontal nystagmus, hypertension (blood pressure 151/112 mm Hg)</td>
<td>Serum: methoxetamine 0.16 mg/L</td>
<td>Nasal insufflation</td>
</tr>
<tr>
<td>M/21a</td>
<td>Convulsions, sinus bradycardia (heart rate 48 bpm), hyponatremia (127 mmol/L), slightly increased serum creatine kinase (270 U/L)</td>
<td>Methoxetamine: serum 30 μg/L, urine 408 μg/L, hair (collected 6 weeks after intoxication) 135 and 145 g/mg</td>
<td>Clonazepam Inhalation of vapour heated on a sheet of aluminum foil</td>
</tr>
<tr>
<td>M</td>
<td>Slurred and deliberate speech, diminished motor skills, uncontrolled movements</td>
<td>Blood: methoxetamine 10 ng/mL; carboxy-THC, clonazepam, 7-aminoclonazepam, diphenhydramine, MDMA</td>
<td>Elian and Hackett (2014)</td>
</tr>
</tbody>
</table>

Fatal intoxication

<table>
<thead>
<tr>
<th>Case</th>
<th>Symptoms</th>
<th>Methoxetamine Levels</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>M/26</td>
<td>Pulmonary edema</td>
<td>Femoral blood: methoxetamine 8.6 μg/mg venlafaxine 0.3 μg/g O-desmethylvenlafaxine</td>
<td>Wikström et al. (2013)</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>0.4 μg/g</th>
<th>0.00009 μg/g</th>
<th>0.00003 μg/g</th>
<th>0.00005 μg/g</th>
</tr>
</thead>
<tbody>
<tr>
<td>AM-694</td>
<td>AM-2201</td>
<td>JWH-018</td>
<td></td>
</tr>
</tbody>
</table>

Wiegrowski et al. (2014)


a. Patient admitted consumption of approximately 500 mg of 'methoxetamine, 750 mg of benzofury' and 1.5 L of beer.
b. Patient admitted consumption of approximately 200 mg of 'methoxetamine powder'.
c. Patient admitted consumption of 50–100 mg of 'methoxyketamine 99.9% – research chemical'.
d. Patient admitted injection of approximately 100 mg of 'methoxetamine' and consumption of codeine tablets 3 h later.
e. Patient admitted consumption of approximately 50 mg of 'methoxetamine'.

It has to be emphasized that in addition to methoxetamine, other psychoactive compounds and their metabolites have also been detected in the blood/serum samples of intoxicated subjects, including MDMA (Elian and Hacket, 2014 and Hofer et al., 2012), carboxy-Δ9-tetrahydrocannabinol (carboxy-THC) (Elian and Hacket, 2014), AM-2201 (Wikström et al., 2013), clonazepam and 7-aminoclonazepam (Elian and Hacket, 2014); diphenhydramine, venlafaxine and desmethylvenlafaxine (Wikström et al., 2013 and Wood et al., 2012a), derivatives of 1-benzofuran: 5-APB/6-APB (Wood et al., 2012a). Treatment of these intoxication cases was supportive, with the administration of benzodiazepines (for sedation), anti-emetics, intravenous fluids (for dehydration), and physical restraints and respiratory support as required.

More than 20 deaths due to methoxetamine overdose have been disseminated. In all these cases, the presence of methoxetamine was analytically confirmed. It should be noted that the conducted postmortem analysis also revealed the presence of other psychoactive drugs of abuse, such as alcohol, THC, MDA, amphetamines, MDMA, cocaine, synthetic cannabimimetics, ketamine, APB, and opioids (Chiappini et al., 2014, EMCDDA, 2013b, Wiegrowski et al., 2014 and Wikström et al., 2013).

6. Analytical methods for determination and measurement of methoxetamine

The last decade has witnessed an alarming increase in the number of novel psychoactive compounds introduced to the drug market as alternatives of controlled substances of abuse. This phenomenon was accompanied by an urgent need to develop fast and effective analytical methods for qualitative and quantitative measurements of new drugs in products, and more importantly in biological samples. At present, the most common are chromatographic methods with mass spectrometric detection. First measurements of methoxetamine concentration in human blood used gas chromatography–mass spectrometry (Shield et al., 2012; Wood et al., 2012a). Recently, liquid chromatography with electrical ionization ion-trap tandem mass spectrometric detection (LC-EI-IT-MS-MS) has been developed for measurement of methoxetamine in human blood, urine, and vitreous body (Abe et al., 2013, Al-Saffar et al., 2013, De Paoli et al., 2013 and Soh and Elliott, 2014). Furthermore, a technique established and validated by Abe et al. (2013) allowed to couple LC-EI-IT-MS-MS with an on-line automatic sample preparation using a Turbo-Flow device. The mass spectrum of methoxetamine contains the parent protonated [M + H]+ ion at m/z 248. The most intense ion product was observed at m/z 203 (Abe et al., 2013, Al-Saffar et al., 2013 and De Paoli et al., 2013), a much weaker signal was found at m/z 175 (Al-Saffar et al., 2013 and De Paoli et al., 2013). Methoxetamine was found to be stable over 21 days in blood and plasma (Soh and Elliott, 2014) or 3 months in urine (Al-Saffar et al., 2013) stored at room temperature.

7. Conclusions

Methoxetamine is a new designer drug with a wide range of effects, some of which resemble and others greatly vary from effects of similar hallucinogenic/dissociative compounds, ketamine, and phencyclidine. The consumption of methoxetamine carries a significant health risk. A great deal of research is still needed to fully quantify the short- and long-term effects of methoxetamine and its interaction with other drugs of...
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abuse.

Conflict of interest

The author declares that there are no conflict of interest.

Transparency document

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