Methoxetamine (MXE)

Critical Review Report

Agenda item 5.9

Expert Committee on Drug Dependence

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World Health Organization

Contents

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Summary

Methoxetamine (2-(3-methoxyphenyl)-2(N-ethylamino)-cyclohexanone) is a new synthetic drug derived from ketamine and belongs to the arylcyclohexylamine class. Methoxetamine has dissociative properties. The mechanism of action is through N-methyl D-aspartate (NMDA) receptor antagonism and the inhibition of serotonin reuptake. It is described to show longer lasting and more powerful effects than ketamine but with weaker analgesic and anesthetic effects.

Main effects of methoxetamine are hallucinations, depersonalization and dissociation of the physical body.

Adverse effects following methoxetamine consumption have been reported to be vomiting, nausea, diarrhoea, hypertension, tachycardia and, in some cases, central nervous system depression. Although various non-fatal and fatal intoxications involving methoxetamine have been reported in the literature, they also involved other drugs and manners of death.

In animals methoxetamine shows abuse potential.

1. Substance identification

A. International Nonproprietary Name (INN)

None

B. Chemical Abstract Service (CAS) Registry Number

1239943-76-0 free base
1239908-48-5 hydrochloride salt

C. Other Names

MXE
3-MeO-2-Oxo-PCE
2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone;
2-(3-methoxy-phenyl)-2-(ethylamino)-ciklohexanone;
2-(ethylamino)-2-(3-methoxyphenyl)cyclohexan-1-one;
methoxyphenylethylamino-ketocyclohexane.
Common names or codenames that have also been reported are: MXE100 and metoksetamiini (Finnish).
The name 'methoxetamine' was reported to have been coined as a contraction of methoxy-ketamine.

D. Trade Names

Not applicable.

E. Street Names

Hypnotic, Jipper, Kmax, Kwasqik, legal Ketamine, Lotus, MA, Magic, MEX, Mexxy, Minx, M-ket, MXE, , Panoramix, Roflcoptr Special K, and. Special M, X, Ultraviolet and Zeolite.

F. Physical properties

The hydrochloride salt of methoxetamine is a white, odourless crystalline powder at room temperature. A physical description of the base form could not be found in readily accessible literature.

G. WHO Review History

During its 36th meeting, the WHO Expert Committee on Drug Dependence discussed the critical review report[1] on methoxetamine and concluded that owing to the current insufficiency of data regarding dependence, abuse and risks to public health, methoxetamine should not be placed under international control at this time but be kept under surveillance.

In 2014 the European Union decided to bring methoxetamine under control after a risk assessment by the EMCDDA. [2,3] Furthermore new information on its abuse

potential and more (non) fatal accidents warranted an update of the critical review report on behalf of the 37th ECDD.

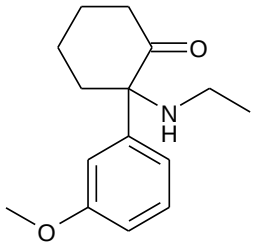
2. Chemistry

A. Chemical Name

IUPAC Name: (RS)2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone
CA Index Name: N/A

B. Chemical Structure

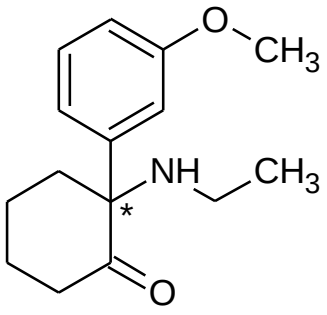
Free base:



Molecular Formula: $C_{15}H_{21}NO_2$
Molecular Weight: 247.33 g/mol (Monoisotopic mass: 247.157)
Melting point: 227-233°C (hydrochloride salt)
Boiling point: 389,084°C at 760 mm Hg

C. Stereoisomers

Two enantiomers, the chiral center is marked with a star below. Methoxetamine is commonly available as the racemic mixture.



D. Synthesis

The synthesis of methoxetamine was achieved by 4 steps through simple reactions involving an aromatic nitrile, a Grignard reagent, bromination, imine formation through reaction with a suitable amine, followed by the application of heat to the product to allow ring expansion of 1-[(ethylimino)(3-methoxyphenyl)methyl]-1-cyclopentanol.[4]

E. Chemical description

Methoxetamine is an arylcyclohexylamine substance which shares some structural similarities to ketamine. In methoxetamine, the 2-chloro group on the phenyl ring and the N-methylamino group of ketamine have been replaced by a 3-methoxy and a N-ethylamino group respectively.

F. Chemical properties

Methoxetamine hydrochloride (salt) is soluble in organic solvents like ethanol (10 mg/mL) at 25° C, DMSO (14 mg/mL) and dimethyl formamide (5 mg/mL) and in aqueous, nonorganic solvents like PBS (5 mg/mL).

G. Chemical identification

Hayes et al.[4] reported the synthesis and analysis of MXE. They used NMR, FTIR and GC-MS to describe the structure of methoxetamine.
In a factsheet of the Belgium Early Warning System reference is made to the identification and the analytical profile of methoxetamine using GC-MS, LC-MS and LC-MS/MS.[5]

3. Ease of convertibility into controlled substances

Methoxetamine is not readily converted into other controlled substances.

4. General pharmacology

A. Pharmacodynamics

Roth *et al.*[6] used the resources of the National Institute of Mental Health "Psychoactive Drug Screening Program" to obtain a neurochemical profile of methoxetamine and to compare it with those of ketamine and PCP. The results confirmed that methoxetamine has significant affinity for glutamate NMDA receptors.

The pKi values for phencyclidine, ketamine and methoxetamine are 7.23 ± 0.07, 6.18 ± 0.07 and 6.59 ± 0.06 respectively. Interaction with the NMDA receptor is thought to be the key factor underlying the mechanism of action of ketamine, phencyclidine and other dissociative anaesthetics and may explain their psychotomimetic effects in human users.

Furthermore methoxetamine binds to the serotonin transporter (SERT) with a pKi of 6.32 ± 0.05. Ketamine does not bind to the serotonin transporter. As the affinity of methoxetamine for SERT is quite similar to its affinity for the NMDA receptor, it is not unlikely that inhibition of SERT may contribute to both its psychopharmacological profile and the additional features seen in acute methoxetamine toxicity.

B. Routes of administration and dosage

Methoxetamine is generally administrated orally, by insufflation, or injected (both intramuscular and intravenously). Rectal and sublingual administration have also been reported.

The dosage is ranging from 20–100 mg insufflated, 40–100 mg orally and 10–80 mg when injected intramuscularly. In Table 1 (below) an overview of onset and duration of effect after various routes of administration is shown.

Table 1**:** Methoxetamine onset and duration of effect [7]

	Sublingual/buccal	**Insufflated**	**Intramuscular**
Onset	10 – 20 minutes	10 – 20 minutes	2 – 10 minutes
Coming up	15 – 30 minutes	15 – 30 minutes	10 – 20 minutes
Plateau	60 – 120 minutes	60 – 120 minutes	40 – 90 minutes
Coming down	60 – 120 minutes	60 – 120 minutes	30 – 120 minutes
Total duration	3 – 5 hours	2.5 – 4 hours	2 – 3 hours
After effects	2 – 48 hours	2 – 48 hours	2 – 48 hours

C. Pharmacokinetics

So far there have only been two studies that have investigated the metabolism of methoxetamine. No studies have assessed other pharmacokinetic parameters such as absorption, distribution or excretion.

By using their standard urine screening approaches Meyer *et al*.[8] could identify the phase I and II metabolites of methoxetamine in both rat and human urine. A total of eight metabolites were described allowing postulation of the following metabolic pathways: *N*-deethylation, *O*-demethylation, hydroxylation, as well as combinations hereof, followed by glucuronidation or sulfation. The initial metabolic step in humans, the *N*-deethylation, was catalyzed by CYP2B6 and CYP3A4. Menzies *et al*.[9] used human liver microsomal cell preparations and human urine in order to identify the phase I and II metabolites of methoxetamine.The following metabolites were described in the *in vitro* studies: normethoxetamine, *O*-desmethylmethoxetamine, dihydromethoxetamine, dehydromethoxetamine and several structural isomers of hydroxymethoxetamine and hydroxynormethoxetamine. Phase II glucuronide conjugates included those of *O*-desmethylmethoxetamine, *O*-desmethylnormethoxetamine and *O*-desmethylhydroxymethoxetamine. In urine collected from three individuals presenting with acute methoxetamine toxicity the presence of the majority of these phase I and II metabolites was also confirmed. With the exception of the absence of the *O*-desmethylhydroxynormethoxetamine metabolite in all three of the patient urine samples. This may be due to this metabolite being conjugated or to other factors such as the timing of the urine collection relative to methoxetamine consumption. There was also concordance in the Phase II metabolites between the *in vitro* and *in vivo* samples.

N-desethylmethoxetamine or normethoxetamine was the most abundant metabolite with a response relative to methoxetamine of 100%; *O*-desmethylmethoxetamine and hydroxynormethoxetamine were present with a response relative to methoxetamine of 73 % and 14 % respectively. The other metabolites all had relative responses of less than 1 %.

5. Toxicology

Toxicity in Animals

There are no published pre-clinical safety data available concerning the toxicity, reproductive impact and carcinogenic/mutagenic potential of methoxetamine. Dargan *et al*.[10] used a mouse model that has previously been used to investigate the chronic urinary tract toxicity associated with ketamine.[11]

The study was undertaken to investigate whether methoxetamine was causing the same damage to the urinary tract as ketamine does. Two-month-old mice were administered either 30 mg/kilograms of methoxetamine per day (n=5) or saline control (n=3) by intraperitoneal injection for three months.

In all the mice which were administered methoxetamine, degeneration in both the proximal and distal convoluted tubules of the kidney and inflammatory cell infiltration of the kidneys was observed. Mononuclear cell infiltration in the submucosal layer and in the muscle layer of bladder was also observed. None of the above histological changes were seen in mice administered the saline control.

In summary, this study demonstrated that three months of daily 30 mg/kg intra-peritoneal methoxetamine resulted in significant urinary tract in mice. The changes in the kidney and the bladder are similar to those that were seen in comparable animal models of chronic ketamine administration.

It looks as if methoxetamine is not the 'bladder friendly' alternative to ketamine, as suggested on the internet.

Toxicity in Humans

No studies were identified that have examined the toxicity of methoxetamine in humans. Lawn *et al*. [12] used a survey to look at changes in prevalence of methoxetamine use in time (2011 and 2012) and between countries (USA and UK) and they also investigated the prevalence of urinary symptoms in the group of methoxetamine users, who had also used ketamine at least once in their lifetime.Of the methoxetamine users 23.0% ($n = 98$) reported experiencing urinary symptoms. Prevalence of at least one urinary symptom was related to frequency of methoxetamine use in the last month. However, previous ketamine use cannot be ruled out as the cause of the symptoms.

6. Adverse reactions in humans

For drugs of abuse there is no formal registration system for adverse events. Information can be obtained by surveys, by searching on internet and by collecting information from national poison information services.

The following adverse events of methoxetamine use have been mentioned: [13-15]

Cardiovascular System:

- Tachycardia, hypertension

Central Nervous System:

- impaired or loss of consciousness, coma
- cerebellar ataxia, slowed psychomotor performance, dysarthria, disoriented
- confusion, hallucinations
- agitation and aggression
- dissociative psychosis (temporary)[16]

Miscellaneous:

- pyrexia
- nystagmus

Non-fatal intoxications

A total of 120 non-fatal intoxications were reported by the EU Member States to the Early Warning System. Of these, analytical confirmation of the presence of methoxetamine in biological samples was reported in 55 cases: Belgium (1), France (3), Italy (13) and Sweden (38).

In addition to the non-fatal intoxications reported earlier by EU Member States, 16 non-fatal intoxications were identified in the scientific and medical literature. Of these, analytical confirmation of the presence of methoxetamine in biological samples was reported in 12 cases: France (1), Poland (2), United Kingdom (7), Switzerland (1) and the US (1).

Regarding the 38 analytically confirmed cases reported by Sweden, 11 were methoxetamine alone and 27 were "mixed poisonings" involving one or more psycho-active substances including ethanol. The frequency of symptoms for both groups is shown in table 1. Poisoning severity scores for the 11 methoxetamine only cases were mild (7), moderate (2) and severe (2) and for the 27 mixed methoxetamine / other psycho-active substance(s) cases were mild (11), moderate (10), severe (3) and unknown (3).

Table 2: Clinical features reported in the 38 analytically confirmed non-fatal intoxications reported by Sweden.[17]

Symptom	Methoxetamine only (n=11)	Mixed methoxetamine / other psycho-active substance(s) (n=27)
Hypertension	36%	48%
Tachycardia	36%	44%
Hallucinations	27%	22%
Nystagmus	27%	26%
CNS depression	27%	44%
Mydriasis	27%	30%
Anxiety	18%	19%
Muscular symptoms	18%	11%
Agitation / restlessness	9%	33%

Only in 15 cases methoxetamine was analytically confirmed to be the only psycho-active substance present. Unfortunately, most of these cases lack important details as gender, age and blood levels as shown in Table 3.

Table 3: What is known of the 15 cases in which methoxetamine was the only psycho-active substance present.

Country	Patient/age	Biological sample	MXE results	Other substances	Notes
Belgium	?	Urine	+	Not detected	
France	?	Blood, Urine	30 µg/L (plasma) 408 µg/L	Not detected	
France	?	Hair	+	Not reported	?
France[18]	M, 21	Blood, Urine, Hair	30 µg/L (serum) 408 µg/L 135 and 145 pg/mg *	Not detected	* two 2.5 cm hair strands
Sweden	?	Blood, Urine	+	Not detected	11 cases

Fatal intoxications

There have been 22 deaths reported on methoxetamine either to the EU Early Warning System or in the literature in which there was analytical confirmation of methoxetamine in post-mortem biological samples: Austria (1), Finland (1), France (1), Norway (1), Poland (2), Sweden (1) and the United Kingdom (15). An overview is given in Table 4.

Table 4: Reported deaths in which methoxetamine was analytical confirmed in post-mortem biological samples.

Country	Patient/Age	Biological sample	MXE concentration	Other substances	Notes
Austria	?	?	+		Cause of death reported as central circulatory failure due to methoxetamine overdose
Finland	?	Blood	5200 mg/mL	olanzapine (0.24 mg/L) citalopram (0.20 mg/L) clozapine (0.13 mg/L)	Death by drowning
France	M, 38	Blood	9.48 µg/mL		Cause of death reported as asphyxia
Norway [19]	F,	Blood	0.064 mg/L	AH-7921 (0.33 mg/L) etizolam (0.27 mg/L) phenazepam (1.33 mg/L), 7-aminonitrazepam (0.043 mg/L), diazepam (0.046 mg/L), nordiazepam (0.073 mg/L), oxazepam (0.018 mg/L)	Cause of death reported as intoxication with AH-7921 in combination with other psychoactive drugs.
Poland [20]	M, 29	Blood, Urine	5.8 µg/mL * 85 µg/mL		* calculated as vial was destroyed during transport
Poland [21]	M, 31	Blood Urine Hair	0.32 µg/mL 4.36 µg/mL Negative	amphetamine 0.06 µg/ml in blood, 0.27 µg/ml in urine 0.19 µg/g in hair	Cause of death reported as acute poisoning as a result of methoxetamine and amphetamine.
Sweden [22]	?	Femoral blood	8.6 µg/g	AM-694 AM-2201 JWH-018 cannabis venlafaxine	Cause of death reported as suspected acute intoxication with methoxetamine although the presence of the three synthetic cannabinoids may have contributed to the death.
United Kingdom	F, 27	Blood	+	6-APB (2460 ng/mL)	Case of death was reported as ingestion of 6-APB and methoxetamine

Country	Patient/Age	Biological sample	MXE concentration	Other substances	Notes
United Kingdom	M, 17	Blood, urine, vitreous humour	+	alcohol 80 mg/100 ml in blood 146 mg/100 mL in urine, 109 mg/100 mL in vitreous humour	Cause of death was reported as drowning, with methoxetamine ingestion noted as a contributory factor.
United Kingdom	M, 20	?	0.22 mg/L		Cause of death was reported as drowning
United Kingdom	M, 25	Blood, urine, vitreous humour	+	dihydrocodeine alcohol 80 mg/100 ml in blood, 146 mg/100 mL in urine 155 mg/100 mL in vitreous humour	Cause of death was reported as drowning, with methoxetamine ingestion noted as a contributory factor.
United Kingdom	M, 27	Blood, Urine	0.03 mg/L	amitriptyline (0.13 mg/L) cocaine (0.44 mg/L) diazepam (4.27 mg/l) and metabolites MDMA (0.20 mg/L, MDA	Case of death was reported as mixed drug toxicity
United Kingdom	M, 29	Blood	+	EDDP (645µg/L) mirtazapine (69 µg/)	Cause of death was reported as drug overdose
United Kingdom	M, 41	Blood, Urine	+ (in urine)	methiopropamine (1.74 mg/L) MDA (0.18 mg/L) alcohol 7 mg/100 ml in blood 16 mg/100ml in urine	Cause of death was reported as natural causes (ischaemic heart disease and coronary artery atheroma)
United Kingdom	M, 43	Blood	0.89 mg/L (unpreserved) 1.1 mg/L (preserved)	methiopropamine (2.8 mg/L in unpreserved blood)	Case of death was reported as methoxetamine and methypropamine toxicity
United Kingdom	?	Blood	+	Fluoromethcathinone MDMA Methylone MDAI MDPV 5-IAI AMT	
United Kingdom	?	Not reported	+		6 deaths

7. Dependence potential

A. Animal Studies

No studies were identified that have examined the dependence potential of methoxetamine in animals.

B. Human Studies

No studies were identified that have examined the dependence potential of methoxetamine in humans.

Self-reported experiences on user websites suggest compulsive re-dosing as well as the unintentional consumption of more than was initially planned. A possible explanation for this behavior is that methoxetamine has a longer delay in onset than ketamine which might lead to a high risk of re-dose.

8. Abuse potential

A. Animal Studies

Botanas *et al*. [23] tried to determine the relative abuse potential of methoxetamine (MXE) in comparison with ketamine (KET) by employing self-administration (SA) and conditioned place preference (CPP) paradigms in Sprague-Dawley rats. By using these models both rewarding and reinforcing effects can be studied. Also the effect on locomotor activity during the conditioning phase of the CPP was looked at.

They demonstrated that rats in the SA test showed modest self-administration of MXE (0.25, 0.5, 1.0mg/kg/infusion), while KET (0.5mg/kg/infusion) was robustly self-administered. Furthermore MXE (2.5 and 5mg/kg) induced significant CPP in rats, the effect being comparable to that of KET (5mg/kg). But, MXE did not produce any locomotor alterations while ketamine decreased the locomotor activity of rats.

These results demonstrate that MXE has rewarding and reinforcing effects in rats. Extrapolating these data suggest that MXE has a potential for human abuse.

B. Human Studies

There have been no formal studies investigating the dependence potential or abuse potential of methoxetamine in humans. There are no published reports in the medical literature of individuals with suspected or proven dependency on and/or abuse of methoxetamine.

There is one single report on Erowid, from 2012, of an 18 year old male with an extensive drug-using history from the age of 15, who self-reported ‘addiction’ to methoxetamine. This individual was sent a free 250 mg sample of methoxetamine when he purchased ‘2-CP’. Following initial pleasurable experiences (“state of dissociation and opiate-like

euphoria") with low doses of methoxetamine (25–40 mg per line), he started craving the drug and started using increasing amounts of up to 1 g of methoxetamine per week "doing it all day, low doses in the morning and afternoon culminating into intense trips in the evening" and needing at least 50 mg of methoxetamine to get "threshold effects". When he stopped regular use of methoxetamine, he described feeling "detached and sad". From the information provided in the report there does not appear to have been physical withdrawal symptoms after cessation.

However, it is believed that since methoxetamine shares many similarities with ketamine regarding effects and chemical structure, it might have a similar abuse potential. [13, 24, 25]

9. Therapeutic applications and extent of therapeutic use and epidemiology of medical use

No evidence has been found that methoxetamine has been therapeutically used.

10. Listing on the WHO Model List of Essential Medicines

Methoxetamine is not found on the WHO Model List of Essential Medicines.

11. Marketing authorizations (as a medicinal product)

None known.

12. Industrial use

No evidence has been found that methoxetamine has any legitimate industrial use.

13. Non-medical use, abuse and dependence

The desired psychological and behavioural effects reported on various user websites include: euphoria, empathy, pleasant intensification of sensory experiences, mild to strong sense of dissociation from the physical body, derealisation, improved social interaction, distorted sense of reality, vivid hallucinations. [13, 14, 26]

Undesired psychological and behavioural effects reported by users include disorientation, paranoia, post-use depression, mental slowing, anxiety, difficulty speaking and confusion. [7,13, 26]

It appears from the user reports that the unwanted psychological and behavioural effects occur at similar doses (10–100 mg) to those reported to be used for the desired effects.

14. Nature and magnitude of public health problems related to misuse, abuse and dependence

The global emergence of NPS reported in December 2013, reported data on methoxetamine use from the following countries: Austria, Norway, Canada, Russian Federation, Estonia, Singapore, Finland, Spain, France, Ukraine, Italy, United Kingdom, Netherlands and the United States.

The prevalence of methoxetamine use has been studied by a number of groups using different methods and often over various timeframes (e.g. in the UK, before and after a

temporary ban). The results are shown in Table 5. The prevalence data are quite different per country, which is not uncommon for drugs of abuse/new psychoactive substances. Overall the results give an indication of life-time, last year and last month prevalence for methoxetamine. These are all much lower for methoxetamine when compared to ketamine.

Table 5: Prevalence of methoxetamine (MXE) use in comparison with ketamine (KET).

Country	**Life-time (%)**		**Last year (%)**		**Last month (%)**	
	KET	MXE	KET	MXE	KET	MXE
Australia [27]		0,4		0,2		
NL		3*		2,3*		0,3*
Slovenia [28]				5,2**		
UK [29] 2011-2012	47,5	4,9	24,5	4,2		
UK nightclubs [30]		3		3		2
UK gayfriendly nightclubs [31]	60,3	6,1	48,7	4,8	34,9	1,9

* = lower than the prevalence rate for ketamine

** = 0.4% reporting frequent use (i.e. more than 40 times).

Kinyua *et al*.[32] studied the presence of seven New Psychoactive Substances, including methoxetamine, in sewage samples collected from sewage treatment plants in Belgium and Switzerland. They observed a consistent presence of methoxetamine in most of the sewage samples at levels higher than the lower limit of quantification. The lower limit of quantification was between 0.5 and 5 ng/L for all compounds studied.

Using sewage-based epidemiology does not provide an answer on the prevalence of drug use in a population but at least it gives a first indication of the presence of a drug in a certain population.

Triangulating data from different sources show that methoxetamine use is present in a number of regions. Its profile, based on participants' first experience of use, was very similar to that of ketamine. But almost one-third of users reported that they did not intend to try the drug again.[29]

15. Licit production, consumption and international trade

Not applicable.

16. Illicit manufacture and traffic and related information

The seizures of methoxetamine reported, from countries worldwide, have typically encountered the substance in powder form and the amounts are normally in milligram-gram quantities. In total, multi-kilogram amounts of methoxetamine in powder form have been seized. In addition, methoxetamine in tablet form have been seized in several countries and includes preparations of methoxetamine alone and in combination with a wide variety of other drug substances.

The distribution and trafficking mainly occurs through the Internet. No specific reports on the licit and illicit production are available.

17. Current international controls and their impact

Methoxetamine is not controlled under the United Nations conventions.

18. Current and past national controls

On September 25th the Council of the European Union has decided to bring methoxetamine under control. Before October 2nd 2015 all Member States should have brought the subject under control with regard to their national legislation.

Furthermore, methoxetamine is a controlled substance in Japan, Switzerland, Turkey and Russia.

In the United States, methoxetamine is not controlled under the Controlled Substances Act (CSA).

19. Other medical and scientific matters relevant for a recommendation on the scheduling of the substance

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