Methoxetamine-related deaths in the UK: an overview

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ABSTRACT

Methoxetamine (MXE) is a novel ketamine derivative. Its effects resemble those induced by dissociative anaesthetics, but are stronger and longer-lasting compared to ketamine. Here we focus on cases related to MXE that were reported to the *national programme* on Substance Abuse Deaths (*np*-SAD). The Programme receives information on drug-related deaths from Coroners in the UK and Islands and other data suppliers on a voluntary basis, following completion of inquests or other legal inquiries. Eight cases in which MXE was found at post-mortem and/or directly implicated in the death and/or mentioned in the Coroner's verdict are described. The deaths occurred between August 2011 and January 2013, and the median age at death was 27 years old; with the majority of White ethnicity (6/8); and male (7/8). MXE was used together with other substances in 7/8 cases. MXE was found at post-mortem in all cases, and implicated in the deaths of seven. Of particular interest is that drowning was the mechanism of death in three cases.

Presented here is the largest known UK case series of MXE fatalities. MXE consumption appears to be an issue of concern because, even though it is perceived as safe by young users, its use can induce adverse physiological and psychological effects and even cause death, including through its effects on risk perception. Since MXE was typically identified in combination with other drugs in this case series, it is difficult to describe the exact role that MXE played in the reported fatalities.

KEY WORDS: MXE; methoxetamine; novel psychoactive substances; NPS; death; designer drugs; legal high; drug misuse.

BACKGROUND

Methoxetamine (MXE) is a ketamine derivative which began being used recreationally in the UK in 2010 [1]. As with other novel psychoactive substances, known as "legal highs" or "designer

drugs", which are chemicals often designed to be similar in their psychoactive effects to controlled drugs [2-4], its effects and toxicity are not fully understood [5,6]. Although classified as a Class B drug in February 2013 [7], it is still widely marketed online in the UK [8]. The Mixmag/Guardian Global Drugs Survey of UK respondents (n=7770) reported that 4.9% of respondents had used MXE with 6% of regular 'clubber' respondents also reporting use of MXE [9].

MXE is a more powerful and less anesthetising analogue of ketamine [10,11]. It acts as an N-methyl-D-aspartate (NMDA) receptor antagonist and a dopamine reuptake inhibitor and is thought to increase the release of serotonin [12]. Oral doses of MXE between 20 to 100mg after 40 minutes have effects that last for 5-7 hours. Doses of 5 to 50mg injected or insufflated achieve effects after minutes, lasting for 1-2 hours [13]. MXE effects are dose dependent and include: euphoria; hallucinations [14]; and dissociative anaesthesia [15]. Adverse effects include: nausea; cardiovascular symptoms; cognitive impairment [16]; and paranoia [17]. MXE toxicity may manifest itself as the ketamine-like dissociative state [18,19], with hyper activation symptoms [20-22] and cerebellar signs [13,23]. MXE is not known to be associated with bladder dysfunction, as is typical with the regular use of ketamine [6,24,25], but this requires verification.

At the time of writing, there are no reference values of MXE toxic or fatal blood concentrations. Wood [25] reported blood concentrations of 90ng/ml (0.09mg/L); 120ng/ml (0.12mg/L); and 200ng/ml (0.20mg/L) of serum in intoxication cases, in which respectively 200mg; 500mg; and an unknown quantity had been ingested. Hydzik [18] reported a case of acute MXE poisoning of a patient who took the drug for suicidal purposes, and whose MXE serum concentration was 450ng/ml (0.45mg/L). Wikstrom [26] reported an accidental fatal intoxication with MXE in Sweden, with blood concentration of MXE of 8.6ug/g (8.6mg/L), in a male with a history of depression and drug abuse. To our knowledge, there are no publications in the academic literature regarding a series of MXE-related fatalities.

METHODS

Fatalities involving MXE were extracted from the *np*-SAD database, which has been collecting and analysing drug-related deaths in the UK and Islands since 1997 and which contains more than 29,000 cases, with Coroners and relevant regional authorities submitting information voluntarily on drug-related deaths. Since 2004, *np*-SAD has been receiving information also from the Scottish Crime and Drug Enforcement Agency and the General Register Office for Northern Ireland. The information submitted includes statements from witnesses, family and friends; general

practitioners' records; authorities' reports; clinical reports; post-mortem or toxicology reports; and other inquest information. Information sourced from searches of media websites and newspapers is also used to supplement the data provided. Full details of the *np*-SAD data collection form and its surveillance work can be found in the Programme's annual report [27].

For a case to qualify as a 'methoxetamine-related death' for the purposes of this case series, it had to fulfil one or more of the following criteria: MXE either implicated in the cause of death; mentioned in the Coroner's verdict; or found in post-mortem toxicological analysis.

A literature search on "Methoxetamine", "Methoxetamine effect*", "Methoxetamine toxicity", "recreational use of dissociative anaesthetic*", "legal high*", "novel psychoactive substance*", "designer drug*", "Methoxetamine fatal*", was carried out on PubMed, PsycINFO, Embase and Medline databases. No other UK MXE fatalities were identified.

CASE HISTORIES

Case histories are summarised in Table 1. MXE was found in the post-mortem toxicological screening of all eight cases, and was considered to have caused or contributed to the deaths of seven of these. The cases consisted of seven males and one female; with a median age at death of 27 years. Seven out of the eight reported deaths occurred in England, with one (Case 7) occurring in Northern Ireland. In seven cases MXE was used together with other substances. Besides MXE, post-mortem screening detected: alcohol in three cases; methiopropamine (MPA) in two; and the following drugs each found once: dihydrocodeine; methadone; mirtazapine; 6-(2-aminopropyl)benzofuran or 1-benzofuran-6-ylpropan-2-amine (6-APB, also known as "benzofury"); 3,4-Methylenedioxyamphetamine (MDA); Tetrahydrocannabinol (THC); cocaine; 3,4-methylenedioxy-N-methylamphetamine (MDMA or "ecstasy"); amitriptyline; and diazepam. MXE was ruled to have contributed to the death of seven cases. Presented below are brief summaries of each death.

Case 1

In August 2011, a 29 year old male, who was known to be a drug abuser and was prescribed methadone, was found dead at home. Post-mortem toxicology revealed the presence of methadone; mirtazapine; and MXE, which were all considered implicated in the death. The death was deemed accidental and due to a drug overdose.

Cases 2 and 3

In January 2012, two males, one 25 years old and one 17 years old, both without known psychiatric history or previous drug use, were found submerged in a pond, in unknown circumstances. In both decedents, post-mortem blood screening detected alcohol and MXE. Toxicological analysis of Case 2's blood and urine also revealed the presence of dihydrocodeine. MXE was considered the only drug implicated in the deaths, with both recorded as due to accidental drowning, with MXE ingestion a contributory factor.

Case 4

In January 2012, a 43 year old male was found dead at his home address. The deceased had no known drug history; was not prescribed any psychoactive medication; but was overweight and had a history of epilepsy and high blood pressure. Toxicological analysis of post-mortem blood found MXE and MPA, with the cause of death being "Methoxetamine and Methypropamine toxicity" as a result of misadventure.

Case 5

In March 2012, a 20 year old male student was found dead in the sea. His drug use history was unknown, and it was not known if he was prescribed any psychoactive medication. MXE was the only drug detected and implicated in the death. The cause of death was drowning, and the verdict declared "Open".

Case 6

In September 2012, a 27 year old female, who had suffered with depression and had a history of drug overdoses, but was not prescribed any psychoactive medication, took 6-APB and MXE. She called paramedics, but was declared dead upon arrival at hospital. Both drugs were detected by post-mortem toxicology, and the cause of death was recorded as “Ingestion of 6-APB (benzofury) and methoxetamine” with undetermined intent.

Case 7

In September 2012, a 41 year old male was found dead at home. Adrenaline; citalopram; HIV medication; sildenafil; prochlorperazine; MXE; alkyl nitrite (“Poppers”); MPA; and MDA were found at the scene. He was a known drug abuser, and was not prescribed psychoactive medication. Post-mortem blood screening detected MPA; MDA; MXE; and alcohol. None of the drugs was considered implicated in the death. The cause of death was ischaemic heart disease and coronary artery artheroma, and the Coroner recorded a verdict of “substantial natural heart disease in a recreational drug user”.

Case 8

In January 2013, a 27 year old male with a history of depression and anxiety was found dead at home. He was prescribed pregabalin; temazepam; and tramadol and was known to abuse alcohol; cocaine; cannabis; and pharmaceutical medication. It is understood he was with his friends the night before. Several empty alcohol containers were found throughout the property, along with blister packs of pregabalin tablets (54 missing); tramadol tablets (10 missing); temazepam tablets (14 missing); and remnants of a white crystalline powder. Toxicological analysis of his blood found: MXE; benzoylecgonine; MDMA; amitriptyline; diazepam; alcohol; THC; and MDA. The cause of death was recorded as mixed drug toxicity, and the intentionality of the deceased was deemed undetermined.

DISCUSSION

To the best of our knowledge, this paper provides information relating to the only case series of MXE-related fatalities in the scientific literature. Only two other MXE-related fatalities have been previously reported, and the post-mortem blood serum concentrations for the cases were 0.45mg/L [18] and 8.6ug/g (8.6mg/L) [26]. MXE was considered implicated in both deaths. The levels of MXE found were provided in two cases in which MXE was implicated in combination with other drugs, with blood concentrations of 0.89mg/L and 0.03mg/L. In a further case, the level of MXE found was 0.22mg/L, but the tissue type was not specified.

Of the cases presented here, 7/8 died either from drowning or from polysubstance abuse. MXE is likely to affect cognitive function, which may have resulted in the occurrence of the drowning cases. It is of interest that drowning has already been frequently described in association with ketamine-related fatalities [28].

Another point of interest here is that in 7/8 cases, more than one drug was used, principally stimulants; alcohol; or other central nervous system depressants such as benzodiazepines. It appears that toxic reactions such as seizures or arrhythmias may occur when consuming MXE in combination with other drugs. Recent reports and articles on MXE refer to its increasing usage [3]. This may be a cause for concern, because it is not widely controlled outside the UK, hence it is still easily available to vulnerable individuals. More research needs to be conducted into its health effects and toxicity potential. Health care professionals should be made aware of the potential health harms of MXE, in order to develop early intervention measures and minimise the number of MXE-related poisonings and fatalities.

STUDY LIMITATIONS

In most cases, MXE was identified in combination with other drugs; hence, it is difficult to describe here the exact role that MXE played in the reported fatalities. Due to the voluntary nature of reporting to *np*-SAD and the inquest procedures associated with most drug-related deaths, other MXE-related deaths may have occurred prior to the publication of this case series but have not yet been reported to the Programme as the inquests into such cases may have not yet been concluded. The number presented here should therefore be regarded as the minimum number of MXE-related deaths in the UK.

Declaration of interest

No conflict of interest.

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Table 1: Main characteristics of *np*-SAD methoxetamine-related deaths, UK, 2011-2013

	Date of death (mm/yyyy)	**Age**	**Cause of death**	**Verdict**	**Post-mortem tissue type**					
					Blood	Urine	Unknown/ other specified			
			1a.	1b.	2.					
Case number (Gender)	**1** (M)	08/2011	29	Drug overdose	-	-	Died as the result of an accident	Methadone 0.645mg/L; EDDP +; mirtazapine 0.69mg/L	EDDP +; mirtazapine +	MXE +
	2 (M)	01/2012	25	Drowning	-	MXE ingestion	Misadventure	Alcohol 80mg/dL; dihydrocodeine +; MXE +	Alcohol 146mg/dL; dihydrocodeine +; MXE +	Ethanol Vitreous humour 155mg/dL
	3 (M)	01/2012	17	Drowning	-	MXE ingestion	Misadventure	Alcohol 80mg/dL; MXE +	Alcohol 146mg/dL; MXE +	Ethanol Vitreous humour 109mg/dL
	4 (M)	01/2012	43	MXE and MPA toxicity	-	-	Misadventure	MXE 0.89mg/L (blood plain); 1.1mg/L (blood preserved); MPA 2.8mg/L (blood plain), + (blood preserved)		
	5 (M)	03/2012	20	Drowning	-	-	Open			MXE 0.22mg/L
	6 (F)	09/2012	27	Ingestion of 6-APB and MXE	-	-	Open	6-APB 2.46ug/L; MXE +		
	7 (M)	09/2012	41	Ischaemic heart disease	Coronary artery atheroma	-	Substantial natural heart disease in a recreational drug user	MPA 1.74mg/L; MDA 0.18mg/L; alcohol 7mg/dL	MPA +; MDA +; MXE +; Alcohol 16mg/dL	
	8 (M)	01/2013	27	Mixed drug toxicity	-	-	No inquest (Open)*	Amitriptyline 0.13mg/L; benzoylecgonine 0.44mg/L; diazepam and metabolites 4.27mg/L; MDMA 0.20mg/L; MDA +; MXE 0.03mg/L; THC +		Amitriptyline gastrojejunal (g-j) low level; diazepam and metabolites g-j 9mg; MDMA g-j 3mg; MXE g-j low level; Cocaine nasal swabs +; MDMA nasal swabs +; MXE nasal swabs +

+ Positive drug screening result
* No inquest was undertaken, however the intent of the death was deemed undetermined