Methoxetamine associated reversible cerebellar toxicity: Three cases with analytical confirmation

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Context. There have been recent concerns about increasing use and accessibility of methoxetamine, a ketamine derivative. Few data are available to describe the clinical features associated with methoxetamine exposure. We report three cases that presented to hospital with acute neurological toxicity associated with analytically confirmed methoxetamine exposure. Case details. A 19-year-old male presented with severe truncal ataxia, nystagmus, incoordination and reduced conscious level several hours after nasal insufflation of what was initially thought to be ketamine. Features of cerebellar toxicity persisted for 3–4 days before gradual recovery. Two more patients aged 17 and 18 years presented with severe cerebellar ataxia, imbalance and reduced conscious level 40 minutes after nasal insufflation of methoxetamine (MXE). Both had slurred speech, incoordination and cerebellar ataxia that resolved within 24 hours. Serum methoxetamine concentrations were 0.24 mg/L, 0.45 mg/L and 0.16 mg/L, respectively, and no other drugs were identified on an extended toxicological screen. Discussion. Methoxetamine may cause rapid onset of neurological impairment, characterised by acute cerebellar toxicity. Spontaneous recovery was observed, but the duration of recovery may extend to several days. Presentation with an acute cerebellar toxidrome should alert clinicians to the possibility of methoxetamine exposure.

Keywords Acute toxicity; Ketamine; Methoxetamine; Nervous system; Recreational drug

Introduction

Methoxetamine is one of a number of novel psychoactive substances (legal highs) that are available for purchase via the internet in the United Kingdom and elsewhere.1–3 It is an N-ethyl ketamine derivative 2-(3-methoxyphenyl)-2-(ethylamine)cyclo-hexanone and is associated with a number of slang names including ‘MXE’, ‘m-ket’, ‘K-max’, ‘special K’ and ‘mexxy’. It is suggested that methoxetamine may avoid cystitis and bladder dysfunction, which are well characterised complications of long-term ketamine use.4

In view of its structural similarity to ketamine, methoxetamine is thought to act primarily on N-methyl-D-aspartate receptors and by inhibition of dopamine reuptake, although data from pharmacological studies are lacking.5 It is currently not subject to control under the Misuse of Drugs Act in the United Kingdom or similar legislative controls elsewhere in Europe or North America.6–8 Few data exist concerning the clinical effects of methoxetamine use, and attribution has been hampered by a lack of analytical confirmation and concomitant exposure to other substances.1,5,6

There has been one small series of three patients with analytically confirmed methoxetamine toxicity that presented with dissociative symptoms and sympathomimetic toxicity.3 The present paper describes three patients that presented to the Emergency Department of York Hospital after isolated methoxetamine toxicity that were characterised by similar symptoms in addition to significant reversible cerebellar toxicity, and supported by analytical confirmation.

Case 1

A 19-year-old male presented with severe incoordination and dysarthria. He reported having occasionally used ketamine and took what was thought to be ketamine by nasal insufflation 4–5 hours prior to hospital attendance. After this, he had fallen uncontrollably and felt uncoordinated and very drowsy. There was no past history of any significant illness or prescribed medications. Physical examination found a white powder on his nose and extensive bruising overlying the extensor surfaces of both knees. Conscious level was impaired, Glasgow Coma Score 13, and he was disoriented and had severe cerebellar ataxia, coarse nystagmus and slurred speech. Pupils were dilated, there was coarse dysdiadochokinesis, limb reflexes were normal and symmetrical and plantar responses were flexor. Temperature was 36.7°C, heart rate 107 per minute and blood pressure...
A resting electrocardiogram (ECG) showed sinus tachycardia and PR interval 148 ms, QRS duration 101 ms, QT interval 333 ms and QTc (QT corrected by Bazett’s formula) 396 ms. Serum electrolytes, creatinine and liver biochemistry were normal, and creatine kinase was 701 U/L (reference range 40–320 U/L). White cell count was 19.8 × 10^9/L and neutrophils were 17.6 × 10^9/L, and haemoglobin, platelet count, coagulation screen and blood film appearances were normal. Serum carbamazepine and phenytoin concentrations were undetectable (< 0.3 mg/L).

The haemodynamic disturbance resolved within 2–3 hours, and the patient gradually recovered conscious level and cerebellar ataxia slowly resolved over 8–12 hours. No specific treatment was administered. At 48 hours after admission, his gait had significantly improved and vertical nystagmus had resolved, although horizontal nystagmus and fine motor incoordination of the upper limbs persisted. Repeat creatine kinase activity was 2271 U/L at 13 hours after ingestion, 1643 U/L at 29 hours and 1324 U/L at 36 hours. By day 4, the features of cerebellar toxicity had fully resolved and the patient was discharged from hospital.

Case 2

A 17-year-old male reported nasal insufflation of ‘MXE’, which had been supplied by a friend. He had not previously used this agent, and there was no prior recent history of illicit drug use. There was no past history of any significant illness or prescribed medications. Within 20 minutes of drug exposure, the patient reported feeling ‘drunk’ and ‘spaced out’. His coordination became significantly impaired, and he repeatedly fell over before losing consciousness. He was discovered outdoors by a passer-by and an ambulance was summoned. On presentation to the Emergency Department, he had reduced conscious level (Glasgow Coma Score 7), and was responsive only to painful stimuli, temperature 36.7 °C, heart rate 72 per minute, and blood pressure 148/112 mmHg. Speech was slurred, and there was minor horizontal nystagmus, impairment of upper limb coordination and truncal ataxia. Blood pressure normalised within 3 hours of arrival at hospital, and no specific treatment was administered. Clinical symptoms and signs of cerebellar toxicity resolved over a period of 16 hours, and the patient was discharged from hospital.

Toxicological analyses

Written informed consent was obtained from all three patients for toxicological evaluation of blood and urine samples. Methoxetamine was determined by single ion monitoring using gas chromatography–mass spectrometry (Shimadzu UK, Milton Keynes, United Kingdom), and calibrated between 0.005 mg/L and 1 mg/L using known concentrations of methoxetamine (LGC Standards, Middlesex, United Kingdom) and pyribenzamine as an internal standard. Qualitative screening was performed in the full scan mode (m/z range, 30–500), and would have been expected to detect any one of a wide range of different acidic or basic drugs, ethanol and drugs of abuse including 3,4-methylenedioxymethamphetamine, 3,4-methylene-dioxy-N-methylamphetamine, benzodiazepine metabolites and ketamine. Serum methoxetamine concentrations in cases 1, 2 and 3 were 0.24, 0.45 and 0.16 mg/L, respectively, and the corresponding interval after exposure was 4, 2 and 2 hours, respectively. Apart from methoxetamine, an extended urine toxicology screen did not detect ethanol or other chemicals or drugs.

Discussion

Previous cases of presumed methoxetamine intoxication in the literature have largely focussed on symptoms relating to activation of the sympathetic nervous system and the ketamine-like dissociative state, which we too observed. However, our case series highlights the potential for significant toxicity associated with methoxetamine use, with cerebellar ataxia, incoordination, dysarthria and nystagmus being prominent features in all three cases with no plausible alternative explanation. The prolonged duration of toxicity in case 1 cannot be explained by higher methoxetamine concentrations, and the explanation is uncertain. Nystagmus and tremor have been reported in earlier cases. It should be noted that there was no analytical confirmation of methoxetamine in one of these, and in another, the presence of 3,4-methylenedioxymethamphetamine (MDMA) was also detected, and this may have contributed to the observed features. Vertigo and cerebellar ataxia have been described as adverse effects of methoxetamine in an internet forum for recreational drug users. Spontaneous resolution of symptoms and signs occurred. Earlier cases report recovery within 24 hours, which is similar to that observed in cases 2 and 3. However, toxicity may be
persist over several days, as in case 1, and methoxetamine users report that recovery is more prolonged than those associated with ketamine.\textsuperscript{1,3,6} While the clinical features of methoxetamine might be expected to be similar to those of ketamine, the latter has not been reported to cause significant cerebellar toxicity.\textsuperscript{10} Furthermore, the patient in case 1 implied that the clinical effects of methoxetamine were subjectively very different to his prior ketamine use.

This is only the second small case series of analytically confirmed acute methoxetamine intoxications. The present concentrations (0.16, 0.24, 0.45 mg/L) are similar to serum values reported previously (0.09, 0.12, 0.20 mg/L) using the same analytical method in the same laboratory. Given the small number of cases, there remains a lack of reliable data concerning the clinical effects and mechanisms of toxicity of methoxetamine.\textsuperscript{3} However, based on the existing data, methoxetamine seems capable of causing a ketamine-like dissociative picture, with features of sympathomimetic activation, and acute cerebellar toxicity. The present findings should alert clinicians to the possibility of methoxetamine exposure as a cause of cerebellar ataxia in individuals who present to the Emergency Department.

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**Declaration of interest**

The authors report no declaration of interest. The authors alone are responsible for the content and writing of the paper.

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