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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Acute toxicity associated with the recreational use of the ketamine derivative methoxetamine

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Abstract
Purpose Long-term regular use of ketamine has been reported to be associated with severe symptomatic urinary tract problems. Methoxetamine, an arylcyclohexylamine derivative of ketamine, is marketed as a "bladder safe" derivative of ketamine, and no cases of acute toxicity following analytically confirmed methoxetamine use have been reported to date. We report here a case series of three individuals with acute toxicity related to the analytically confirmed use of methoxetamine.

Case series Three patients aged between 28 and 42 years presented to the Emergency Department (ED) on unrelated occasions having used methoxetamine. Clinical features were suggestive of a "dissociative/catatonic" state similar to that seen with ketamine; in addition, they had clinical features of acute sympathomimetic toxicity with significant tachycardia and hypertension. All were managed with low-dose benzodiazepines and discharged home once their symptoms/signs had settled.
Toxicological screening Serum collected at the time of presentation to the ED was analysed qualitatively and quantitatively by gas chromatography–mass spectrometry. Serum concentrations ranged from 0.09 to 0.2 mg/L; in addition, detectable levels of 6-APB/5-APB were found in one of the patients.
Conclusions These three analytically confirmed cases demonstrate that acute methoxetamine-related toxicity is associated with both "dissociative" and "sympathomimetic" clinical features. The information from these three cases is useful to clinical pharmacologists, not only in managing individuals with acute methoxetamine toxicity but also in advising the appropriate legislative authorities on the risk of acute harm related to methoxetamine use. Further work is needed to determine whether methoxetamine is more "bladder friendly" than ketamine, as has been suggested by those marketing methoxetamine.

Keywords Methoxetamine · Ketamine · Acute toxicity · Recreational drug

DW and PD have acted as scientific advisors to the UK Advisory Council on the Misuse of Drugs (ACMD) and the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA).

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Introduction

Recreational use of ketamine is common throughout Europe and the USA [1, 2]. In addition to the risks of acute

ketamine toxicity associated with recreational use, there have been increasing reports of urinary tract pathology, including haematuria, painful micturition and frequency/urgency secondary to interstitial cystitis, developing in individuals using ketamine chronically [3–10].

Methoxetamine, 2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone (3-MeO-2-Oxo-PCE), is an arylcyclohexylamine derivative of ketamine [11]. It is a designer drug that was specifically developed by a UK-based research chemist as an alternative to ketamine, and it is not currently controlled in Europe or the USA. While there have been no formal human or animal pharmacological studies, it has been suggested that methoxetamine is both an *N*-methyl D-aspartate (NMDA) receptor blocker and a dopamine reuptake inhibitor. It has also been suggested that due to the *N*-ethyl group, chronic use of methoxetamine has a lower risk of being associated with the ketamine-related urinary tract pathology described above—however, there is currently no evidence to confirm whether this is the case [12].

There is one reported case of acute toxicity related to the self-reported use of methoxetamine, although there was no analysis of biological samples to confirm that this individual had actually used methoxetamine [13]. Numerous studies in both Europe and the USA have shown that the actual content of psychoactive substances in novel psychoactive drugs available on the Internet and from high street head shops and street level dealers is variable [14–17]. It is therefore important, from both a clinical and law enforcement perspective, that the description of the acute toxicological profile associated with the use of novel psychoactive substances is supported by confirmatory toxicological analytical screening. We describe here three cases of acute toxicity related to the recreational use of methoxetamine, with analytical confirmation of methoxetamine use.

Case series

Case one

A 42-year-old male was found "collapsed" in the street by a member of the public. On arrival in the Emergency Department (ED) he was noted to be drowsy, with a Glasgow Coma Score (GCS) of 6/15, tachycardic (heart rate 135 bpm), hypertensive (blood pressure 187/83 mmHg) and pyrexial (temperature 38.2°C). Some "white powder" was noted in and around his nostrils, consistent with nasal insufflation of a recreational drug. He was managed with a nasopharyngeal airway for airway support; his drowsiness improved over the next 2 h, and his heart rate, blood pressure and temperature also returned to normal limits. On further questioning he reported that prior to his collapse he had drank three pints (approximately 1.5 L) of beer (approximately 6–8 units) and snorted 0.75 g of "benzofury" and 0.5 g of "methoxetamine". He reported that he had purchased both of these drugs from an Internet supplier of research chemicals. He was treated with 5 mg oral diazepam and discharged home later that day when his symptoms and physiological features had settled.

Case two

A 29-year-old male presented having been found "catatonic" by his mother, with a tremor, visual hallucinations, confusion and dilated pupils. On arrival in the ED he was noted to be confused, with a GCS of 14/15, tachycardic (heart rate 121 bpm) and hypertensive (blood pressure 201/104 mmHg). His neurological examination, apart from his confusion, was normal, including normal tone, normal reflexes and no evidence of spontaneous or inducible clonus. He was treated with 5 mg of oral diazepam and admitted for observation overnight; he required no further treatment. The following morning, he was reviewed by the clinical toxicology team and was medically fit for discharge home. At this time, he admitted that he had purchased 2 g of "methoxetamine powder" from an Internet-based supplier of "research chemicals"; he had dissolved approximately 200 mg of this powder in water and drank this prior to becoming unwell. He described the desired effects of methoxetamine as "hallucinogenic" and similar to those he had experienced when he had previously used PCP or ketamine.

Case three

A 28-year-old male was brought into the ED from a local nightclub having been found collapsed in the bathroom; en route to the ED he developed worsening agitation and aggression. On arrival in the ED he was drowsy, with a GCS of 10/15, confused and significantly agitated. He was tachycardic (heart rate 113 bpm) and hypertensive (blood pressure 198/78 mmHg) and had dilated pupils. His temperature was normal (36.9°C). There was some "white powder" around his nostrils, consistent with nasal insufflation a recreational drug, and he had a bag of white powder on him that was labelled as "methoxetamine". He was treated with 5 mg intramuscular of midazolam, and his agitation, confusion and physiological features settled within 3 h. When his symptoms had settled and prior to being discharged home, he admitted purchasing the methoxetamine from a high-street "head shop" prior to use.

Toxicological screening

Informed consent was obtained from all three patients for toxicological screening of blood (serum) samples collected

at the time they were reviewed by one of the ED physicians/clinical toxicologists. Screening for methoxetamine and general drugs of abuse was achieved by injecting 1 μL of the sample extract onto a gas chromatography–mass spectrometry (GC–MS) system (Shimadzu Scientific Instruments, Kyoto, Japan). Electron impact ionization (EI) was used. Qualitative screening was performed in the full scan mode (*m/z* range 30–500). Helium was used as the carrier gas and an HP-5MS column (30 m × 0.25 mm; film thickness 0.5 μm) for separation (Hewlett-Packard, Palo Alto, CA). The injector port was held at 225°C. The initial column temperature was set at 80°C and held for 4 min prior to being ramped by 20°C/min up to 280°C, held for 5 min and then ramped by 40°C/min up to 290°C and held for a further 15 min. Methoxetamine eluted at 13.64 min. Quantitation of methoxetamine, purchased from LGC Standards (Teddington, Middelsex, UK), was achieved by a SIM (single ion monitoring) on a Shimadzu GC–MS system over a calibration range of 0.005 to 1 mg/L. An isocratic temperature programme of 220°C for 9.5 min was used, with methoxetamine (190 *m/z*) eluting at 5.84 min. Pyribenzamine was used as an internal standard (91 *m/z*), eluting at 7.32 min. The serum methoxetamine concentrations ranged from 0.09 to 0.2 mg/L (Table 1). The results of other substances detected in this extended toxicological screen are shown in Table 1.

Discussion

The three patients reported in this case series had all intentionally purchased methoxetamine, either from Internet research chemical suppliers or from a high-street "head shop". One individual was reported to have developed a catatonic state and the other two were described as having been found "collapsed". In these two latter patients, it is possible that a dissociative or catatonic state may have been mis-interpreted as a reduced level of consciousness. On presentation to the ED, all three patients had evidence of sympathomimetic toxicity, with marked tachycardia and hypertension. Use of methoxetamine was analytically confirmed in all three patients, with serum concentrations ranging from 0.09 to 0.2 mg/L. One patient (case 1) also reported the use of "benzofury" in addition to the methoxetamine. Analytical screening detected not only the presence of methoxetamine, but also that of either 1-benzofuran-6-ylpropan-2-amine (6-APB) or 1-benzofuran-5-ylpropane-2-amine (5-APB). Unfortunately, at this time we are not able to differentiate between 6-APB and 5-APB analytically. It has been suggested that "benzofury" contains 6-APB. There have been no previously reported cases of analytically confirmed use of 6-APB/5-APB.

Table 1 Serum and urine toxicological screening results for the three cases

Case	Age (years), sex	Serum methoxetamine concentration (mg/L)	Other drugs detected
1	42, male	0.12	5-APB or 6-APB
2	29, male	0.09	Diphenhydramine and venlafaxine
3	28, male	0.2	Midazolam

5-APB, 6-ABB, 1-Benzofuran-5-ylpropan-2-amine and 1-benzofuran-6-ylpropan-2-amine, respectively

There has been only one previously published case of acute toxicity related to the self-reported use of methoxetamine [13]. The patient described in this case report injected methoxetamine powder purchased from an internet supplier and then presented to the ED with agitation and appeared to be in a dissociative state; the patient did not have hypertension or tachycardia as described in our three patients. The authors subsequently purchased what they believed to be the same product on the Internet, and subsequent analysis of this powder purchased at a different time revealed that it contained methoxetamine. The main, and significant limitation, of this case report is that there was no analysis of biological samples obtained from the patient to confirm that his presentation was actually related to the use of methoxetamine. There are numerous reports demonstrating an inconsistency in the actual content of psychoactive substances in novel psychoactive drugs available on the Internet [14–17], and therefore it is entirely possible that this patient had not actually used methoxetamine. Conversely, we can be certain that methoxetamine was used and was responsible for the clinical features seen in the three patients described in our case series as the presence of methoxetamine was analytically confirmed in all three patients.

There are increasing reports of bladder toxicity, including haematuria secondary to interstitial cystitis, developing with the long-term use of ketamine, particularly from the Far East and Hong Kong where the prevalence of ketamine use is greater [3–10]. It is thought that this toxicity relates to the inflammatory properties of ketamine metabolites [18]. There is also the suggestion that the use of the *N*-ethyl group in methoxetamine was chosen so that it was less likely to be associated with the chronic bladder toxicity associated with ketamine [12]; however, no animal or in vitro studies have yet been conducted to determine whether or not this is the case. Furthermore, methoxetamine has not been used recreationally for long enough to determine if there is actually a lower risk of bladder-related toxicity with the use of this drug. Therefore, in our opinion, at this time there is no evidence to support the suggestion that methoxetamine is associated with a lower risk of chronic bladder-related toxicity than ketamine.

Our three cases of analytically confirmed acute toxicity associated with use of methoxetamine show that the acute toxicity profile includes both ketamine-like "dissociative/catatonic" symptoms and sympathomimetic features (hypertension and tachycardia). There have been no formal pharmacokinetic or pharmacodynamic studies investigating the properties of methoxetamine. However, it has been suggested that methoxetamine is both an NMDA receptor blocker and a dopamine reuptake inhibitor [11]. These pharmacological properties may explain the pattern of acute toxicity that we have described in our patients, with both typical "ketamine-like" dissociative symptoms, along with significant agitation/aggression and sympathomimetic features of hypertension and tachycardia.

We believe that, on the basis of these cases and the increasing evidence of the availability of methoxetamine in high street head shops and on Internet legal high sites, attention should be directed to the classification of methoxetamine.

References

1. European Monitoring Centre for Drugs and Drug Addiction (2010) Annual report 2010: The state of the drugs problem in Europe. Available from: www.emcdda.europa.eu/attachements.cfm/att_120104_EN_EMCDDA_AR2010_EN.pdf. Accessed 25 Oct 2011
2. United Nations Office on Drugs and Crime (2011) World drug report 2011. Available from: www.unodc.org/documents/data-and-analysis/WDR2011/World_Drug_Report_2011_ebook.pdf. Accessed 25 Oct 2011
3. Chu PS, Kwok SC, Lam KM, Chu TY, Chan SW, Man CW, Ma WK, Chui KL, Yiu MK, Chan YC, Tse ML, Lau FL (2007) 'Street ketamine'-associated bladder dysfunction: a report of ten cases. Hong Kong Med J 13:311–313
4. Chu PS, Ma WK, Wong SC, Chu RW, Cheng CH, Wong S, Tse JM, Lau FL, Yiu MK, Man CW (2008) The destruction of the lower urinary tract by ketamine abuse: a new syndrome? BJU Int 102:1616–1622
5. Colebunders B, Van Erps P (2008) Cystitis due to the use of ketamine as a recreational drug: a case report. J Med Case Rep 2:219
6. Shahani R, Streutker C, Dickson B, Stewart RJ (2007) Ketamine-associated ulcerative cystitis: a new clinical entity. Urology 69:810–812
7. Tsai TH, Cha TL, Lin CM, Tsao CW, Tang SH, Chuang FP, Wu ST, Sun GH, Yu DS, Chang SY (2009) Ketamine-associated bladder dysfunction. Int J Urol 16:826–829
8. Wood D, Cottrell A, Baker SC, Southgate J, Harris M, Fulford S, Woodhouse C, Gillatt D (2011) Recreational ketamine: from pleasure to pain. BJU Int 107:1881–1884
9. Mak SK, Chan MT, Bower WF, Yip SK, Hou SS, Wu BB, Man CY (2011) Lower urinary tract changes in young adults using ketamine. J Urol 186:610–614
10. Kalsi SS, Wood DM, Dargan PI (2011) The epidemiology and patterns of acute and chronic toxicity associated with recreational ketamine use. Emerg Heal Threat J 4:7107
11. UK Advisory Council on the Misuse of Drugs (ACMD) (2011) Consideration of the novel psychoactive substances ('legal highs'). Available from: http://www.homeoffice.gov.uk/publications/agencies-public-bodies/acmd1/acmdnps2011?view=Binary. Last accessed 25 Oct 2011
12. Morris H (2011). Interview with a ketamine chemist: or to be more precise, an arylcyclohexylamine chemist. Vice Magazine 11 Feb 2011. Available from: www.vice.com/read/interview-with-ketamine-chemist-704-v18n2. Accessed 25 Oct 2011)
13. Ward J, Rhyee S, Plansky J, Boyer E (2011) Methoxetamine: a novel ketamine analog and growing health-care concern. Clin Toxicol (Phila). doi:10.3109/15563650.2011.617310
14. Davies S, Wood DM, Smith G, Button J, Ramsey J, Archer R, Holt DW, Dargan PI (2010) Purchasing 'legal highs' on the Internet—is there consistency in what you get? Q J Med 103:489–493
15. Ramsey J, Dargan PI, Smyllie M, Davies S, Button J, Holt DW, Wood DM (2010) Buying 'legal' recreational drugs does not mean that you are not breaking the law. Q J Med 103:777–783
16. Brandt SD, Sumnall HR, Measham F, Cole J (2010) Analyses of second-generation 'legal highs' in the UK: initial findings. Drug Test Anal 2:377–382
17. Spiller HA, Ryan ML, Weston RG, Jansen J (2011) Clinical experience with and analytical confirmation of "bath salts" and "legal highs" (synthetic cathinones) in the United States. Clin Toxicol (Phila) 49:499–505
18. Yeung LY, Rudd JA, Lam WP, Mak YT, Yew DT (2009) Mice are prone to kidney pathology after prolonged ketamine addiction. Toxicol Lett 191:275–278