Out with the old, in with the new? Case reports of the clinical features and acute management of two novel designer drugs

E J Hamilton & G P Misselbrook

Abstract

Methoxydine (4-MeO-PCP) and Methoxetamine (3-MeO-2-Oxo-PCE) are both commercially produced designer drugs with structural and biochemical similarities to phencyclidine (PCP). Although phencyclidine toxicity is well documented, its recreational use in present times is rare. With the advent of new designer drugs being available widely through internet sites, Acute Physicians should be aware of the clinical features and management of these potential toxins. We present a case of methoxydine ingestion (which to our knowledge has not been previously documented in any medical journals) and a case of methoxetamine ingestion, and discuss their history, contrasting clinical features and acute management.

Keywords

4-MeO-PCP, 3-MeO-2-oxo-PCE, Phencyclidine, Designer Drugs, Methoxetamine.

Key Points

- Synthetic designer drugs are rapidly emerging and widely available with little known about their clinical and toxicological effects in the acute setting.
- Designer drugs are often synthesised in commercial laboratories and sold openly on the internet. Their chemical structure is often based upon traditional illicit recreational drug compounds, such as phencyclidine (PCP), which may not be commonly encountered in modern clinical practice.
- Acute physicians should have a firm knowledge of how to recognise and manage toxicity due to established recreational drugs if they are to effectively manage patients presenting after consuming these novel agents.
- Due to the criminalisation of designer drugs, chemists are constantly developing novel compounds which can be marketed as legal recreational or 'research' drugs to circumvent drug controls, making the management of toxicity due to these drugs a challenging and rapidly evolving medical concern.

Case 1

A 45 year old man was admitted to the Emergency Department of a large UK teaching hospital after being found disorientated with hypersalivation by his girlfriend. He admitted to taking a new experimental 'legal high' six hours previously which he had ordered from the internet. He had a past medical history of bipolar affective disorder and chronic back pain for which he was taking dihydrocodeine. He had been admitted four months previously after ingestion of the recreational drug 6-(2-aminopropyl) benzofuran (6-APB) – a drug with entactogen/stimulant properties similar to MDMA (ecstasy).

He was admitted to the Acute Medical Unit (AMU) for observation due to his reduced conscious level and disorientation. On assessment in AMU the patient admitted to taking methoxydine, otherwise known as 4-methoxyphencyclidine or 4-MeO-PCP, together with a 1litre bottle of cider. He had taken the drug for recreational use and there was no suicidal intent.

Observations revealed pulse 62bpm, respiratory rate 8 breaths per minute, oxygen saturations of 95% on air, blood pressure 173/116mmHg and temperature 35.8°C. On gross examination, the patient was tremulous with occasional myoclonic jerks. Cardiovascular and abdominal examinations were unremarkable. Neurological examination revealed a normal level of consciousness but scanning speech with dysarthria and nystagmus in all directions of lateral gaze. Pupils were 3mm, reactive and equal bilaterally. The patient was slow to respond to commands but power and sensation were globally intact. Reflexes were brisk globally. In AMU there was no ataxia on finger-nose testing, heel-shin test or dysdiadochokinesia but his gait was documented as ataxic in the emergency department. While his gait was now stable, he was still unable to heel-toe walk. There were no features of acute psychosis or biological features of mania or depression.

Electrocardiogram (ECG) revealed a sinus rhythm with rate 80bpm and normal QTc interval (442ms). Bloods were unremarkable apart from a mildly raised Creatine Kinase (CK) of 200. Urine was sent for a drugs of abuse screen. The immunoassay screen was positive for opiates (detected as dihydrocodeine) and amphetamines but negative for cocaine, benzodiazepines, cannabis and methadone. Gas

Dr E J Hamilton
MBChB, BSc (Hons), MRCP(Acute), PGDipMedEd, Consultant in Acute Medicine, Norfolk and Norwich University Hospital NHSFT

Dr G P Misselbrook
MBBS, MRCP(UK) Core Trainee in ACCS Acute Medicine, Norfolk and Norwich University Hospital NHSFT

Correspondence:
Dr G P Misselbrook
Acute Medicine Unit
Norfolk and Norwich University Hospital
Colney Lane
Norwich
NR4 7UY
Email: garymisselbrook@doctors.org.uk

chromatography revealed an unknown compound, reported as a possible 'legal high'.

The patient was treated conservatively with intravenous (IV) fluids and neurological observations were monitored. The patient was reassessed nine hours after admission and found to be fully conscious and orientated and mobilising normally with only a mild scanning dysarthria. He was discharged home 18 hours after admission.

Case 2

A 30 year old man was brought to the Emergency Department by ambulance after his work colleagues found him acting strangely in his hotel room after playing around 30 matches in a five-a-side football tournament. The paramedics noted him to be agitated, confused and hallucinating. The patient admitted to taking a white substance at around 5pm, given to him by an associate which he had been told was M-KET otherwise known as methoxetamine or 3-MeO-2-Oxo-PCE. He had been drinking alcohol heavily throughout the day. He was normally fit and well but did have a history of occasional recreational drug abuse including ketamine and anabolic steroids.

On examination his temperature was 37.9C, pulse rate 80bpm, respiratory rate of 12 breaths per minute and blood pressure 155/99mmHg. His saturations were 97% on air. His Glasgow Coma Score (GCS) was initially 13/15 (E4V3M6) losing two points for his nonsensical speech. His pupils were dilated to 6mm and reactive to light. He was agitated, hallucinating and talking 'gibberish'. His respiratory, cardiovascular and gastrointestinal examinations were normal.

His ECG was in sinus rhythm with a normal QTc of 380ms. His blood results revealed a markedly increased Creatine Kinase (CK) of 5023units/L. A urine immunoassay screen was later found to be negative for all drugs of abuse but gas chromatography revealed an unknown compound in the amphetamine region which was consistent with Methoxetamine.

He was admitted to AMU as it was felt that he was currently unsafe for discharge given his confused and agitated state. He was reassessed in AMU and his confusion and agitation were much improved. He had full recollection of the events earlier in the day (playing football) and remembered taking the noxious substance although he could not remember much after. His blood pressure had settled to 120/90 and he was apyrexial. He was steady on his feet and promptly discharged with advice to drink plenty of fluids.

Discussion

In recent years there has been a dramatic increase in the production and use of 'designer drugs'. These are often marketed as 'legal highs' or 'research drugs' and sold over the internet. This is reflected by a doubling in the number of online shops selling 'legal highs' between January and July 2011.[1] These drugs hit the headlines in 2010 when a number of deaths were linked to the compound mephedrone, which has since been classified as a Class B Drug in the UK. Due to the criminalisation of these designer drugs, chemists are constantly developing novel compounds which can be marketed as legal recreational drugs to circumvent drug controls, while still providing the user with the effects of classified illicit drugs. In this case report, we described two patients who ingested legal highs from a similar pharmacological class but which had subtly different biochemical and physical effects. In both cases acute physicians were inexperienced in the management of these recreational drugs.

Table1. Members of the Arylcyclohexamine Class which may or have been used as drugs of abuse.

Bromadol (BDPC)
Benocyclidine (BTCP)*
Eticyclidine (PCE)
Gacyclidine
Ketamine*
Methoxetamine (3-MeO-oxo-PCE)*
Methoxydine (4-MeO-PCP)*
Methoxyketamine*
Phencyclidine (PCP)*
Rolicyclidine
Tenocyclidine
Tiletamine*
3-MeO-PCP*
*confirmed use as illicit drug

Methoxydine (4-MeO-PCP) is a dissociative anaesthetic drug with similar effects to ketamine; both of these drugs are derived from PCP.[2] Methoxetamine (3-MeO-2-Oxo-PCE, mexxy, MXE) is a derivative of ketamine (and therefore of PCP) and has structural features of 3-MeO-PCP[3,4] – a positional isomer of 4-MeO-PCP (methoxydine). PCP, ketamine, methoxydine and methoxetamine all belong to the arylcyclohexylamine (Table 1) class of pharmaceutical experimental drugs and act as both NMDA-antagonists and dopamine re-uptake inhibitors. In lower concentrations the effect of NMDA antagonism is of amnesia and analgesia but in higher concentrations it can cause side effects including hallucinations, paranoid delusions, ataxia, hyper-reflexia, clonus, confusion and agitation.[5,6,7] Dopamine reuptake inhibition can produce stimulant and euphoric effects as well as tachycardia, hypertension, psychosis and aggression.[5,8] Both cases exhibited effects of both NMDA-antagonism and dopamine re-uptake inhibition, although there were clear differences in the clinical effects that the different drugs had on the two patients (Table 2). There is likely a differing ratio in the NMDA-antagonism to dopamine re-uptake inhibition between the two drugs accounting for their range of clinical effects.

Table 2. Clinical features of drug effects in case 1 and case 2.

Case 1	Case 2
Hypersalivation	No change in salivation
Disorientation	Disorientation
Drowsiness	Agitation
No amnesia	Amnesia
No hallucinations	Hallucinations
Myoclonic jerks	No myoclonic jerks
Dysarthria	No dysarthria
Nystagmus	No nystagmus
Hyper-reflexia	Normal reflexes
Gait ataxia	Normal gait
3mm pupils	6mm pupils
Apyrexial (35.8C)	Mild pyrexia (37.9C)
Normal heart rate	Normal heart rate
Hypertension (173/116)	Mild hypertension (155/99)
Depressed respiratory rate (8/min)	Mildly depressed respiratory rate (12/min)
Mildy raised CK 300 units/litre	Raised CK 6000 units/litre*

*This CK may be partially attributed to the significant amount of exercise in which the patient had participated during that day.

Both methoxydine and methoxetamine are relatively novel designer drugs, first marketed in 2008 and 2010 respectively. Although their mechanism of action and potential side effects can be predicted, little is still known of their toxicity and pharmacological profile. Their structure is based on phencyclidine (PCP or 'angel dust') and their action is similar to ketamine. PCP is rarely used as a recreational drug in the modern day but was very popular in the 1960s and 1970s. In the 1970's PCP was described as the primary drug of abuse in the United States, but declined in use throughout the 1980s.[9] It is classified as a Class A Drug in the UK. The presentation of PCP intoxication is with confusion, rage, delusions, amnesia, ataxia and hallucinations.[10] Clinical features include dilated pupils, nystagmus, hypertension and tachycardia. Potential life-threatening effects include seizures, malignant hypertension, respiratory arrest and coma. Ketamine toxicity produces similar toxic effects of agitation, hallucinations, anxiety, psychosis, hypertension and tachycardia.[11]

Given the similarities in chemical structure and physical effects of PCP, ketamine and these novel agents we surmise the management of their intoxication should follow that of these established drugs. Management of the acute toxicity of methoxetamine has previously been documented in a case report and follows supportive measures similar to those of ketamine toxicity.[12] The management of both ketamine and PCP toxicity are similar and include simple ABCDE assessment and management, the use of intravenous fluids to prevent and manage rhabdomyolosis and promote renal excretion of the drug, and benzodiazepines for agitation and seizures.[8,12,13] If high doses of the drug have been ingested within one hour, activated charcoal may be administered.[13] In cases of malignant hypertension, benzodiazepines, sodium nitroprusside or phentolamine can be used, making sure to avoid pure beta-blockade which can lead to unopposed alpha-adrenergic effects and worsening hypertension.[13] Involvement of critical care may be required for ventilatory support in cases of respiratory arrest or for cooling patients if they develop malignant hyperthermia. Phenothiazine's should be avoided as they may exacerbate drug intoxication due to their effects on dopamine receptor inhibition.[11]

In both our cases, the diagnosis was made by a comprehensive history and on the clinical features found on examination. We were fortunate that both patients were able, despite their intoxicated conditions, to provide an accurate history of the drug thought to be ingested. The urine toxicology screen on both patients provided interesting results. However, these results were not available until after the patients were discharged and did not aid the diagnosis.

Although not available to us, point of care rapid urine assays are available for certain drugs of abuse including amphetamines, methamphetamines, barbiturates, benzodiazepines, cocaine metabolites, opiates, PCP, tetrahydrocannabinol (THC), acetaminophen and methadone.[14] False positives may occur if the patient is on certain prescription drugs and the assays will detect drugs used up to 30 days prior to testing.[14] However, combined with the appropriate history and clinical features, urine assays may be a useful diagnostic tool when ingestion of an illicit drug is suspected. There is, however, currently no bedside test available to detect the multitude of legal highs that are widely available. In both of our cases, the presence of a legal high was only detected on gas chromatography, although in case one, the immunoassay was also positive for amphetamine. This may have been a false positive due to the presence of methoxydine.

The consumption of a 'legal high' therefore should be suspected in any patient who is thought to have taken a recreational drug particularly if rapid urine assays are negative for commonly used illicit drugs. The diagnosis is made on clinical grounds and acute physicians should possess sufficient knowledge of the effects of traditional recreational drugs such as PCP. Although the patients were clearly intoxicated, neither suffered any of the life-threatening complications which can be associated with PCP. Both had a short period of observation within the AMU and were managed with supportive measures only.

In conclusion, manufacture and marketing of legal highs is expanding at an unprecedented speed and is a growing health concern. There is limited reliable data for acute physicians managing toxicity caused by these substances and we are likely to encounter an increasing number of cases. The management of patients taking designer drugs or so called 'legal highs' should therefore be extracted from the established drugs from which they are derived. Acute Physicians should therefore have a firm understanding of the presentation and management of the toxicity of these established recreational drugs.

**Subsequent to researching and writing this case report, in March 2012, methoxetamine was referred by the Home Office to the Advisory Council on the Misuse of Drugs (ACMD) for possible temporary controlling. In April 2012, the ACMD placed it under a temporary class drug order, which prohibits its import and sale for 12 months. Methoxydine still remains legal, at the time of publication.

Declaration of competing interests: Nothing to declare.

References

1. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). Online sales of psychoactive substances/'legal highs': summary of results from the 2011 multilingual snapsnots. EMCDDA, Lisbon, November 2011.
2. King LA. New drugs coming our way – what are they and how to we detect them? EMCDDA conference, Lisbon, 6-8 May 2009.
3. Ward J, Rhyee S, Plansky J, *et al*. Methoxetamine: a novel ketamine analog and growing health-care concern. *Clinical Toxicology* 2011; **49:** 874–5.
4. Corazza O, Schifano F, Simonato P, *et al*. Phenomenon of new drugs on the internet: the case of ketamine derivative methoxetamine. *Hum Psychopharmacol* 2012; **27:** 145–9.
5. Pomarol-clotet E, Honey GD, Murray GK, *et al*. Psychological effects of ketamine in healthy volunteers. *British Journal of Psychiatry* 2006; **189:** 173–179.
6. Pender J. Dissociative Anaesthesia. *JAMA* 1971; **215:** 1126-30.
7. Hill SC, Thomas SH. Clinical toxicology of newer recreational drugs. *Clinical Toxicology* 2011; **49:** 705–19.
8. Hofer KE, Grager B, Muller DM, *et al*. Ketamine-like effects after recreational use of Methoxetamine. Ann Emerg Med 2012: published online 12 January 2012.
9. Garey RE. PCP: an update. *J Psychedelic drugs* 1979; **11:** 265–75.
10. McCarron MM, Schulze BW, Thompson GA, *et al*. Acute PCP intoxication: Clinical patterns, complications and treatment. *Ann Emerg Med* 1981; **10:** 290–7.
11. Kalsi SS, Wood DM, Dargan PI. The epidemiology and patterns of acute and chronic toxicity associated with recreational ketamine use. *Emerg Health Threats J* 2011; **4:** online
12. Wood DM, Davies S, Puchnarewicz M, *et al*. Acute toxicity with the recreational use of the ketamine derivative methoxetamine. *Eur J Clin Pharmacol* 2012; **68:** 853–6.
13. Toxbase [www.toxbase.org]. Phencyclidine. [Updated March 2006; cited May 2012] Available at: http://toxbase.org/Poisons-Index-A-Z/P-Products/Phencyclidine/
14. Peace MR, Tamai LD, Potilis A. Performance evaluation of four on-site drug-testing devices for detection of drugs of abuse in urine. *J Anal Toxicol* 2000; **24:** 589–594.