CASE REPORT

Novel psychoactive substances: a novel clinical challenge

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SUMMARY

The recreational use of novel psychoactive substances in the UK has increased markedly within the last decade. The variety of new substances synthesised and sold as 'legal', often under the pretence of being 'plant food' or 'bath salts' is similarly increasing. This presents challenges to clinicians: they may be unaware of these substances or unable to identify them and their potential for complications and drug interactions. This case describes a patient who ingested a novel psychoactive substance and presented with severe agitation following a delay of several days. He experienced renal, hepatic and neurological complications requiring critical care input. Our case adds to the current repertoire of knowledge regarding the effects of ingestion of novel cathinones.

BACKGROUND

Novel psychoactive substances, commonly but often erroneously referred to as 'legal highs', are synthetic compounds which are designed to mimic the pharmacodynamic properties of conventional substances of misuse such as amphetamine ('speed') or MDMA (3,4-methylenedioxy-N-methylamphetamine, 'ecstasy'). While there is little documented historical data detailing use of novel psychoactive substances in the UK, anecdotal reports and data from internet forums suggest the prevalence of novel psychoactive drug use has increased markedly over recent years. A significant proportion of this increase relates to the use of novel synthetic cathinones.^{1 2}

Despite this recent increase in use, synthetic cathinone chemistry is not a new concept. For example, Bupropion (an antidepressant now more commonly prescribed for smoking cessation), marketed as Zyban in the UK, is a synthetic cathinone that has been used in clinical practice since 1985.³ Mephedrone (4-methylmethcathinone) however was the first synthetic cathinone (and first novel psychoactive substance) to become widely publicised and misused in the UK.⁴

The rapid progression in both the prevalence of use of legal highs such as mephedrone and the rate at which new drugs are synthesised poses multiple problems to healthcare professionals and patients alike. Clinical staff are often unfamiliar with newer agents. Additionally, the poor correlation between the 'brand name' of these substances and their actual content makes side effects difficult to predict, yet still potentially lethal.⁵ Novel cathinones have been implicated in deaths both indirectly through complications of multiple drug

ingestion and events such as road traffic accidents and directly with reports of cardiac arrest and severe hyponatraemia following ingestion. This case report illustrates potential side effects of one such novel cathinone, and also brings to light a possible drug interaction with aripiprazole, an atypical antipsychotic that has not been reported previously.

CASE PRESENTATION

A 45-year-old man who had been an inpatient in a psychiatric ward for 6 months was found increasingly agitated and sustained a fall with a dislocated thumb. He had been detained under Section 3 of the Mental Health Act for treatment of his paranoid schizophrenia and mood disorder. During this time his mental state had been stable and he had had no previous episodes of this level of agitation.

On examination, other than having a sinus tachycardia, an apparent dislocation of the left thumb and echymoses on both knees from a fall, no other abnormalities were found.

Drug history included aripiprazole 30 mg daily, sodium valproate 500 mg twice daily and 10 mg diazepam and 7.5 mg zopiclone as required. On inspection of his room, however, a package labelled 'NRG-3' was found. It was reported that he had obtained this substance from an internet website, had it delivered to the ward and taken it 3 days previously.

His psychiatric team became increasingly concerned by his behaviour and referred him to the medical team.

INVESTIGATIONS

Initial blood tests revealed a hyperkalaemia of 6.3 mmol/L (normal range 3.5–5 mmol/L) and hyponatraemia of 129 mmol/L (normal range 135–145 mmol/L), profound acute renal impairment with a creatine of 1032 µmol/L (normal range 75–125), an estimated-glomerular filtration rate (eGFR)/1.73 m² of 5 mL/min (normal >90 mL/min) and a creatine kinase of 93 966 µ/L (normal range <190 µ/L). Liver enzyme aspartate transaminase was markedly raised at 1446 µ/L (normal range 5–35) but with normal bilirubin and alkaline phosphatase. Clotting studies were normal. An ECG showed QT prolongation and peaked T-waves.

A renal ultrasound scan showed increased parenchymal echogenicity compatible with renal impairment and no hydronephrosis, stones or focal masses.

TREATMENT

This patient's life-threatening acute kidney injury was treated in the intensive care unit with an

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aggressive fluid regime and fluid monitoring. An insulin and dextrose infusion was started to treat the hyperkalaemia, and a 1.26% sodium bicarbonate infusion given for 3 days. Discussion was had with the local specialist renal unit as to whether haemofiltration was required, however at the time the patient's renal impairment responded to initial management. The patient was counselled as to the life-threatening nature of his condition but refused treatment, adamant that there was 'nothing wrong' with him. He was therefore treated under the Mental Capacity Act in his best interests. The patient's antipsychotics were stopped pending review of his renal and hepatic function, and one-to-one psychiatric nursing was instituted on the medical ward with regular input from his psychiatric team.

OUTCOME AND FOLLOW-UP

The patient's renal function improved with treatment and creatine kinase fell dramatically on daily monitoring. The patient was eventually discharged with a serum creatine of 329 $\mu\text{mol/L}$ (eGFR 18) and creatinine kinase of 4632 μL . Seven days later at GP follow-up his creatine had reduced to 108 $\mu\text{mol/L}$ (eGFR 64) indicating a substantial recovery in renal function.

DISCUSSION

Synthetic cathinones are artificially engineered derivatives of a psychoactive chemical found naturally occurring in the *Catha edulis* (Khat) plant (2-amino-1-phenylpropanone). Similarly to amphetamine and MDMA they work through binding monoamine transporters for noradrenaline, dopamine and serotonin.⁶ By promoting release of these substances in varying amounts, synthetic cathinones result in increased autonomic stimulation and an enhanced sensation of euphoria and empathy.

In 2011, the Crime Survey for England and Wales estimated the prevalence of use of the synthetic cathinone mephedrone to be 4.4% in 16-year-olds to 24-year-olds. This figure is higher than that for the current use of ecstasy, representing substantial use of novel psychoactive substances amongst young people in the UK.⁷ Unfortunately, as there is no data prior to 2010, when synthetic cathinones became controlled substances, the increase in use is difficult to quantify.

Data from Google analytics shows however, in 2009–2012, a significant increase in search terms 'legal highs', 'plant food' (novel psychoactive substances are frequently sold via the internet as plant food or bath salts) and specific drug names such as

'mephedrone' or 'meow meow' (figure 1). While this does not necessarily represent increased use, it implies an increase in public interest which may be linked to increased ingestion of these substances within this timeframe.

Further data from the European Monitoring Centre for Drugs and Drug Addiction, which records identification of new novel psychoactive substances, reported the highest number of notifications in the European Union so far (49) in 2011 and furthermore that two-thirds of all substances newly reported since 2005 had been during the 2009–2011 period.⁸ Additionally during 2009–2010, calls to Toxbase relating to toxicity among young people in the UK attributable to mephedrone use increased significantly.³

This data suggests that 2009 marks the beginning of a rapid surge of interest in, and synthesis and use of novel psychoactive substances.

There are a number of potential reasons for the rapid increase in synthetic cathinone use seen since 2009. Anecdotal reports suggest that shortages of both cocaine and MDMA during this period, combined with decreased purity of these substances may have contributed in part to the sudden surge in popularity of mephedrone. In addition, during this timeframe, mephedrone was not controlled under the Misuse of Drugs Act, increasing the ease of availability via outlets such as internet websites marketing the substances as 'bath salts' or something similar.

There have been several deaths reported that are directly attributable to ingestion of novel cathinones. In each case patients presented with profound hyponatremia and complications including tonsillar herniation and cardiac arrest. Other side-effects reported to Toxbase include those typically associated with sympathomimetic agents such as agitation, tachycardia, palpitations and insomnia. Interestingly, there were multiple reports of effects lasting more than 72 h after ingestion as seen in the case presented. Clinicians should be aware that complications of these substances can be potentially lethal, and that the onset of these complications can occur days after ingestion of the substance.

Other cases specifically involving renal complications and multiorgan failure as reported here have been documented elsewhere. One case from the USA describes a very similar picture in a patient who ingested the novel psychoactive substance methylenedioxypyrovalerone.⁹ This is a β -keto phenylalkylamine, a synthetic cathinone popular in the USA. The patient

Figure 1 Data showing relative variation in use of Google search terms over time (Data from Google UK).

presented with agitation, had similar ECG changes (widened QTc, peaked T-waves), hyperkalaemia, a raised creatine kinase and abnormal liver function tests. This patient suffered a PEA arrest shortly after admission to hospital, followed by deteriorating neurological function and eventual death shortly after initial presentation. Clinicians felt that this case represented Excited Delirium Syndrome (ExDS). This is a syndrome comprising agitation, hyperthermia, tachypnoea, tachycardia followed by cessation of struggle and eventually cardiac arrest. It is typically seen after ingestion of substances that affect dopaminergic pathways such as cocaine and MDMA and is likely caused by dysregulation of dopamine pathways. It is important that clinicians are alert to early clinical features of ExDS, for instance agitation, tachycardia and electrolyte disturbances and aware that these may occur associated both with the ingestion of 'traditional' drugs of misuse (eg, cocaine and MDMA) and also with synthetic cathinones and other, newer 'legal highs'. These patients have significant risk of clinical deterioration and rapid multiorgan failure and should be managed in a setting that can offer full organ support if required.

The patient was taking aripiprazole, an atypical antipsychotic that is a partial dopamine agonist. The case report from the USA describes a drug history including quetiapine, another atypical antipsychotic that exerts its effects in part through dopamine receptor antagonism. No published data so far explores any potential interaction between novel cathinones and other drugs that affect dopamine regulation such as antipsychotics. It is plausible that this represents a possible novel interaction involving deregulation of dopaminergic pathways with potentially life-threatening complications. Further data is required to establish any interactions between drugs modulating dopamine release and synthetic cathinones.

Considering the rate at which new synthetic cathinones are synthesised, the difficulty in identifying specific substances in the clinical environment and the paucity of existing data it is unlikely that significant progress in establishing drug interactions will be made in a clinically useful timeframe using existing data. Therefore, where cases involving synthetic cathinones have significant complications, clinicians should attempt to identify the culprit substance using toxicology services and report the results to surveillance services such as the National Poisons Information Service in the UK.

The increasing use of novel psychoactive substances poses significant challenges to front line clinicians. A sudden surge in popularity and use of these chemicals compounded by the rapid synthesis of novel substances has resulted in patients presenting that have taken drugs that are difficult to identify, have few published complications and interactions and have lethal complications. Furthermore, the speed at which novel agents are produced results in a paucity of information about drug

interactions available to clinical staff, and, even where complications are known, once other pharmacological agents are taken into consideration we are often left unaware of potentially serious drug interactions.

Learning points

- ▶ The use of novel psychoactive substances has increased dramatically in recent years.
- ▶ These drugs are easy to obtain and are often marketed as 'legal highs' despite many being controlled substances in the UK.
- ▶ These drugs are difficult to identify and often labelled with non-standard names—'street' names no longer reliably correlate with active substances.
- ▶ Side effects of these substances are not well known and potentially lethal: a heightened awareness for unexpected complications is required of clinicians.
- ▶ Toxicological Identification and reporting of suspected complications is required of front-line clinicians in order to build upon the limited body of knowledge in this area.

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