Case series of individuals with analytically confirmed acute mephedrone toxicity

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Context. Previous reports of acute toxicity/harm associated with mephedrone use have been based on self-reported mephedrone use; toxicological screening has not been undertaken in these cases to determine whether mephedrone has been used. Objective. To report the first case series of analytically confirmed mephedrone-related acute toxicity. Materials and methods. Serum samples were collected from individuals presenting to an emergency department (ED) with acute toxicity related to self-reported mephedrone use. Toxicological analysis, by gas-chromatography coupled with mass-spectrometry and liquid chromatography with tandem mass-spectrometry was performed to qualitatively confirm mephedrone use. Symptoms/signs of acute mephedrone toxicity and basic physiological parameters were extracted from the routine ED records. Results. Acute mephedrone-related toxicity was analytically confirmed in seven male patients; the mean ± SD age was 24.6 ± 6.5 years (range 16–36 years). Agitation (four patients) was the most common symptom/sign reported; other common symptoms/signs included: palpitations (two patients); chest pain (two patients); self-limiting pre-hospital seizures (one patient) and headaches (one patient). The mean heart rate was 109.1 ± 21.8 (range 80–140) beats per minute; one patient had a “severe” tachycardia (heart rate of ≥140 bpm). The mean systolic blood pressure was 153.0 ± 39.6 (range 110–210) mmHg; three patients had clinically significant hypertension (systolic blood pressure ≥160 mmHg). Discussion. These analytically confirmed acute mephedrone toxicity presentations had clinical features of toxicity consistent with an acute sympathomimetic toxidrome (e.g. hypertension, tachycardia and agitation). These findings are similar to the pattern of toxicity seen with other sympathomimetic recreational drugs such as 3,4-Methylenedioxymethamphetamine (MDMA) and cocaine. Conclusion. The process for determining whether a novel psychoactive substance should be controlled often relies on demonstrated/proven acute harm associated with its use. It is important that clinical toxicologists undertake appropriate biological sampling and toxicological analyses in suspected cases of “novel psychoactive drug” toxicity. This will ensure that both clinicians and legislative authorities are informed of the confirmed pattern of toxicity associated with these drugs.

Keywords Drugs of abuse; Mephedrone; 4-Methylmethcathinone; Acute toxicity

Introduction

Mephedrone, the commonly used name for 4-methylmethcathinone, is one of a number of synthetic cathinones. There is evidence that mephedrone is sourced from the Internet, often via suppliers based in European Union countries, for supply to users and that supply of mephedrone by street level dealers is also common.¹ Prior to the change in the UK legislation, the supply by these dealers would not be illegal, unless those individuals were mis-selling mephedrone to users as a controlled drug (e.g. amphetamine, cocaine). A survey of over 2000 UK clubbers in 2009 reported that 33.6% of those surveyed believed that they had used mephedrone within the last month, which was comparable with other psychoactive substances such as cocaine, 3,4-Methylenedioxymethamphetamine (MDMA) (“ecstasy”) and ketamine.²

User discussion forums and UK telephone surveys of mephedrone users suggest that the acute toxicity associated with mephedrone use is similar to that seen with other stimulant drugs such as MDMA and cocaine.³,⁴ The recent survey of UK clubbers reported that common unwanted effects included sweating (67% of those who had used mephedrone), headaches (51%), palpitations (43%) and nausea (27%).² In addition, there has been a small case series of patients presenting to an emergency department (ED) with acute mephedrone toxicity reported in the medical literature.⁵

The main limitation of all of these sources of information on the acute unwanted effects/toxicity related to the use of mephedrone is that they are based on self-reporting by users.
of mephedrone that are not substantiated by any analytical confirmation. This is important to note, as there is increasing evidence that legal highs, such as mephedrone, bought off the Internet may not contain the expected active ingredient purchased.\(^6\)\(^-\)\(^8\) We report here the first case series of analytically confirmed mephedrone-related acute toxicity.

**Methods**

**Identification of potential cases**

A convenience sample of individuals presenting to an inner-city ED with self-reported mephedrone use and acute toxicity assumed to be related to mephedrone were reviewed by a clinical toxicologist. Written consent was obtained for detailed toxicological analysis of serum samples to determine whether mephedrone had actually been used.

**Toxicological screening**

Systematic toxicological analysis of serum samples obtained from these patients was undertaken using a combination of gas-chromatography coupled with mass-spectrometry (GC-MS) and liquid chromatography with tandem mass-spectrometry (LC-MS-MS). Analysis was performed to qualitatively confirm the presence of mephedrone. GC-MS was undertaken by chromatographic separation, and was achieved for all derivatives over a 12-minute run. The principle fragment ion for mephedrone was m/z 58. Samples were analysed on a Shimadzu QP2010 gas chromatograph mass spectrometer with an HP5MS column (30 m \( \times \) 0.25 mm, 0.50 \( \mu \)m). LC-MS-MS was undertaken by confirmatory multiple reaction monitoring transitions for mephedrone m/z: 178.2/160.1, 145.1, 119.2. MDMA D5 was used as an internal standard m/z: 199.1/165.0. Chromatographic separation of both compounds was achieved over a 6-minute run. Mobile phase was 50:50 of solution A (95% Methanol, 5% deionised water, Formic acid (1 mL/L) and Ammonium acetate (1 mL/L)) and solution B (100% deionised water, Formic acid (1 mL/L) and Ammonium acetate (1 mL/L)). Lower limit of detection is 0.01 mg/L, with linear range from 0.01 to 1 mg/L.

**Clinical features of acute toxicity**

Information on symptoms/signs of acute mephedrone toxicity prior to and/or on presentation to the ED, along with basic physiological parameters on presentation, were extracted from the routine ED records.

**Results**

Toxicological screening confirmed that mephedrone had been used in seven of the nine individuals recruited. Mephedrone was not detected in the other two patients, but they presented more than 24 hours after mephedrone use and so it is possible that this is the reason that mephedrone was not detected. The results given in the rest of this section are for the seven patients with analytically confirmed mephedrone toxicity.

**Demographics and reported mephedrone use**

Mephedrone was the only drug detected on systematic toxicological analysis in four of the seven patients in this case series. Other drugs detected in the remaining three patients were cocaine (two patients) and a combination of butylone/methylenedioxyprovalerone – (one patient). All of the patients with confirmed acute mephedrone toxicity were males, with a mean \( \pm \) SD age of 24.6 \( \pm \) 6.5 years (range 16–36 years).

The route of mephedrone use was reported by six of the seven patients with analytically confirmed acute mephedrone toxicity: oral ingestion (n = 2), combined nasal insufflation and oral ingestion (n = 2), nasal insufflation (n = 1) and combined oral ingestion and intramuscular injection (n = 1). Mephedrone doses used were reported in mass quantities (mg and/or g) by five individuals; others reported in terms of number of lines or “hits” used. Where the amount used was in mass quantities, the mean \( \pm \) SD (range) amount used was 2.1 \( \pm \) 2.3 (0.3–5.0) g.

**Presenting clinical features and evidence of acute toxicity**

The most common clinical symptom/sign reported prior to or on presentation to the ED was agitation (four patients). Other common symptoms/signs reported included: palpatations (two patients); chest pain (two patients); self-limiting pre-hospital seizures (one patient) and headaches (one patient). No patients had any self-reported skin discouloration or cool/cold peripheries and these features were not noted on clinical review. No patients reported vomiting.

The mean heart rate was 109.1 \( \pm \) 21.8 (range 80–140) beats per minute. Five patients had a tachycardia (pre-defined as a heart rate of \( \geq \) 100 bpm) and one patient had a “severe” tachycardia (pre-defined as a heart rate of \( \geq \) 140 bpm); no arrhythmias were noted. The mean systolic blood pressure was 153.0 \( \pm \) 39.6 (range 110–210) mmHg, and three patients had clinically significant hypertension (pre-defined as a systolic blood pressure \( \geq \) 160 mmHg). The mean temperature was 36.6 \( \pm \) 1.1 (range 35.6–38.1)\(^{\circ}\)C, meaning that no patients in this series had clinically significant hyperpyrexia likely to cause end-organ damage (pre-defined as a temperature of \( > \) 39.0\(^{\circ}\)C).

**Biochemical results**

Serum urea and electrolytes were measured in all patients; serum sodium concentrations were within normal limits in
six patients. Hyponatraemia with a serum sodium concentration of 125 mmol/L was noted in one individual at the time of presentation; plasma and urine osmolalities were consistent with water intoxication and there was no reported recreational or therapeutic use of another drug recognised to cause hyponatraemia and no other drugs were detected in these patients following toxicological screening.

Serum creatinine kinase, as a marker of myotoxicity related to pre-hospital seizures and/or hyperthermia or immobility/unconsciousness with muscle compartment compression, was measured in six patients. It was noted to be raised in one patient at a concentration of 3830 IU/L (upper limit of normal 229 IU/L); there was no evidence that this patient had had a pre-hospital seizure, period of unconsciousness or a period of hyperpyrexia prior to presentation.

**Disposition/clinical outcome**

Four patients were discharged either directly from the ED or from the short-stay observation ward. Of the three patients who required admission to hospital, two patients were admitted for ongoing observation and/or management to a general internal medicine ward and one patient required admission to the intensive care unit (ICU) and subsequently died (clinical details described in next section). Three patients required the use of benzodiazepines (oral and/or intravenous) for the management of agitation. Six patients survived to discharge from hospital with no sequelae noted at the time of discharge; none of these patients represented to the study ED with recurrence of symptoms after discharge. The overall mean ± SD length of stay following presentation to ED of those who survived to discharge was 12.0 ± 10.3 (range 3.4–26.3) h.

**Mephedrone-related fatality**

A 29-year-old male was found collapsed and “unwell” in a local nightclub; limited information was available surrounding the circumstances as he had gone out to the nightclub alone. An unlabelled zip-lock bag containing a white powder was found in his clothing. On arrival in the ED he was noted by medical and nursing staff to have a fluctuating level of consciousness. A CT head scan performed showed evidence of significant cerebral oedema and impending tonsillar herniation. Initial biochemical screening demonstrated hyponatraemia with a serum sodium concentration of 125 mmol/L (plasma and urine osmolalities available later suggested that this hyponatraemia was likely to be the result of water intoxication). He had a witnessed generalised seizure in the ED and was intubated and ventilated and a subsequent CT scan demonstrated that he had tonsillar herniation. He was admitted to the ICU for ongoing supportive management; after discussion with the family treatment was withdrawn. Qualitative ante-mortem toxicological screening confirmed the presence of mephedrone. The powder found with the patient was also confirmed to contain mephedrone. No other recreational drugs were detected on an extended screen of both the powder and biological samples from the patient. Following review of the clinical information, the formal post mortem results and information regarding the events leading up to the individual being found unwell in the nightclub, the coroner determined that the cause of death was: hypoxic brain injury due to cerebral oedema following ingestion of a psychoactive substance. The coroner felt that they were unable to state on the information available that the psychoactive substance was mephedrone, as it was possible that other drugs may have been used which would not have been readily detectable at the time the biological samples were collected (e.g. gamma-hydroxybutyrate or gamma-butyrolactone).

**Discussion**

In this case series of analytically confirmed acute mephedrone toxicity presentations to our ED, we have shown that the clinical features were consistent with an acute sympathomimetic toxidrome (e.g. hypertension, tachycardia and agitation). These findings are similar to the pattern of toxicity seen with other sympathomimetic recreational drugs such as MDMA and cocaine. Additionally, they are similar to that reported in user discussion forums, the UK telephone survey of mephedrone and self-reported mephedrone-related acute toxicity case series.1–5

Mephedrone (4-methylmethcathinone) is a synthetic cathinone which is structurally related to the phenylethylamine family and, therefore, to other stimulant drugs such as MDMA and amphetamine.9 There are currently no data on the mechanism(s) of action but, given its structural similarity to the phenylethylamines, it is likely that these are sympathomimetic in nature. It has been detected in the analysis of substances obtained by law enforcement agencies and substances obtained via Internet purchases since 2007, with its detection increasing over the last 12–18 months.10 It was classified Class B in the UK on 16 April 2010 under the UK Misuse of Drugs Act (1971);11 in addition it is also controlled in a number of other European countries under their drug control legislation.

Despite widespread media reports that mephedrone is sourced from the Internet, studies appear to show that UK users also source it from street-level dealers even before the change in the UK legislation controlling mephedrone in April 2010.1,4 It is available in both powder and tablet/capsule form; the predominant routes of use are through nasal insufflation and oral ingestion.1,4,12

There are no national or European population level surveys that currently collect data on the prevalence of mephedrone use. However, a number of surveys have shown that its use is common in school children, college/university students and clubbers.1,2,4 It is not possible on
the basis of these small population group surveys to determine the true overall prevalence of mephedrone use at this time.

To date, the information on the acute toxicity associated with the use of mephedrone has come from unsubstantiated reports on Internet user discussion forums, population subgroup user surveys and additional case reports and/or case series of self-reported acute mephedrone toxicity presenting to healthcare facilities.\(^1,3-5\) The limitation of all of these data sets for determining whether the adverse effects reported are related to mephedrone is that they are not confirmed by chemical analytical findings. To date, there has only been one confirmed case of isolated mephedrone toxicity;\(^13\) this case series reported here provides additional toxicologically confirmed cases of acute mephedrone toxicity.

The process for determining whether a novel psychoactive drug should be controlled at either a national or European level relies on a number of factors, including demonstrated/proven acute harm associated with the use of the novel psychoactive substance. Therefore, it is essential that clinical toxicologists ensure that appropriate biological sampling and toxicological analysis is undertaken in suspected cases of “novel psychoactive drug” toxicity. This will ensure that the potential for acute toxicity associated with the novel psychoactive substance can be appropriately considered by legislative authorities when considering whether or not to control the drug.

**Declaration of interest:** Dr Paul Dargan and Dr David Wood have acted as expert advisors to the UK Advisory Committee on the Misuse of Drugs and the European Monitoring Centre for Drugs and Drug Addiction.

### References