Clinical characteristics of mephedrone toxicity reported to the UK National Poisons Information Service

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ABSTRACT

Objective To describe the patterns and clinical features of toxicity related to recreational use of mephedrone and other cathinones in the UK using data collected by the National Poisons Information Service (NPIS).

Methods The number of accesses to TOXBASE, the NPIS online poisons information database, details of consecutive cases uploaded onto TOXBASE and the number and details of telephone enquiries made to the NPIS by health professionals in the UK were collected for the period March 2009 to February 2010.

Results Over the year of study there were 2901 TOXBASE accesses and 188 telephone enquiries relating to cathinones, the majority relating to mephedrone (TOXBASE 1664, telephone 157), with a month-on-month increase in numbers. In 131 telephone enquiries concerning mephedrone, alone or in combination with alcohol, common clinical features reported included agitation or aggression (n=32, 24%, 95% CI 18% to 33%), tachycardia (n=29, 22%, 95% CI 16% to 30%), confusion or psychosis (n=18, 14%, 95% CI 9% to 21%), chest pain (n=17, 13%, 95% CI 8% to 20%), nausea (n=15, 11%, 95% CI 7% to 18%), palpitations (n=14, 11%, 95% CI 6% to 18%), peripheral vasoconstriction (n=10, 8%, 95% CI 4% to 14%) and headache (n=7, 5%, 95% CI 2% to 11%). Convulsions were reported in four cases (3%, 95% CI 1% to 8%). One exposed person died following cardiac arrest (1%, 95% CI 0% to 4%), although subsequent investigation suggested that mephedrone was not responsible.

Conclusions Toxicity associated with recreational mephedrone use is increasingly common in the UK. Sympathomimetic adverse effects are common and severe effects are also reported. Structured data collected by the NPIS may be of use in identifying trends in poisoning and in establishing toxidromes for new drugs of abuse.

INTRODUCTION

Mephedrone (4-methylmethcathinone, 4-MMC) is one of several synthetic cathinones structurally related to the naturally occurring phenylpropylamine alkaloid cathinone found in the khat plant (Catha edulis). This is commonly chewed for its stimulant properties in Somalia and Yemen. Cathinones are β-ketoamfetamine derivatives which possess a ketone group at the β carbon position of the amfetamine backbone (figure 1). While cathinone and some of its derivatives are controlled under misuse of drugs regulations in the UK, mephedrone has not been controlled until April 2010 when it became classified as a class B drug. It also remains legal in many other countries worldwide. Synthetic cathinones including mephedrone have been freely available and inexpensive for purchase as research chemicals or plant foods in ‘head shops’ and especially via the internet.

Other than some preliminary data on routes of metabolism in rodents and humans, information currently available about the pharmacology of mephedrone is extremely limited although, as would be expected from their chemical similarity, the properties of other cathinones resemble closely those of amfetamines. However, although it has been suggested that significant structure–activity similarities exist between specific cathinones and their amfetamine analogues, caution should be used in attempting to draw conclusions or make predictions about the activity and potency of individual analogues.

Severe clinical effects and deaths apparently associated with mephedrone have been reported widely in the media although, to date, analytical confirmation of mephedrone exposure has only been established in a few cases. The National Poisons Information Service (NPIS) provides information and advice to health professionals in the UK about the management of poisoning via information held on its website TOXBASE and by answering enquiries made by telephone. Over the last year the NPIS has received increasing numbers of enquiries relating to synthetic cathinones, predominantly mephedrone. This paper describes the epidemiology and clinical effects of poisoning with these agents as reported to the NPIS by the healthcare professionals involved in their care.

METHODS

TOXBASE accesses and telephone enquiry data relating to mephedrone and other synthetic cathinones were sought for the year 1 March 2009 to 28th February 2010. Data for methyleneoxy-methamfetamine (MDMA, ‘ecstasy’) and cocaine were also extracted for comparison.

TOXBASE accesses were quantified for clinical users within the UK, excluding users from Ireland, other overseas countries, the Channel Islands and the Isle of Man. Users within the ‘Educational’ (eg, medical schools) and ‘Government Office’ categories were also excluded, as well as those from NPIS units, to avoid double counting. Accesses were classified into ‘sessions’ to consolidate
multiple instances of the same entry being accessed during the same session.

TOXBASE provides the opportunity for health professionals to upload structured clinical information about exposures, including those involving new or uncommon agents. Information uploaded for cathinones since these entries were added to TOXBASE (table 1) was also collated.

Telephone enquiries to the NPIS are handled by information scientists from the four NPIS units in Birmingham, Cardiff, Edinburgh and Newcastle. Clinical details provided by the enquirer are recorded on the stored on the UK Poisons Information Database which is held on a central server, allowing rapid access to information collected nationally. Data on demographic characteristics (age, sex), severity and clinical features of poisoning relating to mephedrone and other cathinones as recorded by the UK Poisons Information Database. Ethical approval was not required for this study since involved analysis of routinely collected clinical information.

RESULTS

The numbers of telephone and TOXBASE enquiries relating to synthetic cathinones increased steeply over the year of the study, especially those involving mephedrone which has recently become more commonly involved in enquiries than MDMA or cocaine (figure 2). Telephone enquiry numbers for cocaine and MDMA declined over the course of the year.

Over the study period the NPIS handled telephone enquiries from about 188 people reported to be exposed to cathinones (table 1). Of these, 157 involved mephedrone and in 131 (77 males, 49 females, 5 sex not known; median age 20 years) the drug was reported to have been used alone or in combination with alcohol only. In the remaining 26 cases other agents were also reported to be involved, including cocaine (n=13), cannabis (n=6), amphetamine, ketamine, growth hormone, buprenorphine, risperidone, quetiapine and methedrone (n=1 for each).

Details of 27 episodes involving cathinones (23 mephedrone, 4 methedrone) have also been uploaded by health professionals onto TOXBASE. In 18 of these cases (15 males, 7 females, median age 20 years) mephedrone was used alone or with alcohol and in five cases it was used in combination with other agents (cocaine, diazepam, heroin, amphetamine, cannabis, trfluoperazine).

Clinical features reported in the cases involving mephedrone taken alone or in combination with alcohol are shown in table 2. Because the methods of data collection are different, telephone enquiry data and TOXBASE upload data are shown separately. For telephone enquiries, ingestion was more common than insufflation (‘snorting’), while in the cases uploaded to TOXBASE, insufflation was more common although details of route of exposure were often not provided. The median mephedrone dose reported was 1 g for both telephone enquiries (n=30) and TOXBASE reports (n=8). In telephone enquiries the median dose was 1 g for both ingestion (n=19) and insufflation (n=11). In most cases, however, this information was not available or not provided.

The most common clinical features reported by health professionals with mephedrone exposure were those typical for a sympathomimetic agent including tachycardia, palpitations, agitation, anxiety, mydriasis, tremor, fever or sweating and a sympathomimetic agent including tachycardia, palpitations, agitation, anxiety, mydriasis, tremor, fever or sweating and hypertension (table 2). Some patients reported features suggesting peripheral vasoconstriction such as white or blue extremities which were sometimes painful. Other common features included nausea, breathlessness, dizziness and headache. Skin rashes and local effects in the mouth, pharynx or nose were also occasionally reported. Symptoms were often reported to be prolonged after mephedrone exposure (table 2).

Table 1 TOXBASE accesses and telephone enquiries relating to selected stimulants March 2009—February 2010

<table>
<thead>
<tr>
<th>Substance</th>
<th>Synonyms</th>
<th>TOXBASE accesses</th>
<th>Telephone enquiries</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Date of entry on TOXBASE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methedrone</td>
<td>Methoxymethcathinone, bk-PMMA, PMMA, ‘methoxymethcath’</td>
<td>November 2009</td>
<td>3707</td>
</tr>
<tr>
<td>Methamphetamine</td>
<td>bk-MDMA, ‘methylene dyeü’</td>
<td>November 2009</td>
<td>3524</td>
</tr>
<tr>
<td>Methcathinone</td>
<td>ephedrine, m-cat, methcathinone</td>
<td>October 2009</td>
<td>3524</td>
</tr>
<tr>
<td>Ethylene</td>
<td>bk-MDEA, MDEC</td>
<td>No entry</td>
<td>3524</td>
</tr>
<tr>
<td>Butylone</td>
<td>bk-MBDB</td>
<td>No entry</td>
<td>3524</td>
</tr>
<tr>
<td>Methylenedioxy-pyrovalerone</td>
<td>MDPV, hyperfocusine</td>
<td>No entry</td>
<td>3524</td>
</tr>
<tr>
<td>Methylenedioxy-methamphetamine</td>
<td>MDMA, Ecstasy’</td>
<td>Throughout study</td>
<td>3524</td>
</tr>
<tr>
<td>Cocaine</td>
<td></td>
<td>3707</td>
<td>3524</td>
</tr>
</tbody>
</table>
Chest pain was a common symptom; in one case this was associated with ECG changes suggesting acute myocardial infarction. Confusion and/or psychosis were also frequent. Three patients were reported to have generalised convulsions; in one episode this was following an apparent cardiac arrest and in two episodes no prior history of epilepsy was recorded. A further patient was described as having focal convulsions and another patient had undiagnosed blackouts. In other episodes convulsions were not reported but a reduced level of consciousness or in combination with alcohol as reported in telephone enquiries. One NPIS enquiry was made during unsuccessful resuscitation attempts following an apparent cardiac arrest in a patient exposed to mephedrone.

Table 2 - Clinical features reported with exposure to mephedrone alone or in combination with alcohol as reported in telephone enquiries (n=131) or uploaded to TOXBASE (n=18)

<table>
<thead>
<tr>
<th>Clinical features reported in telephone enquiries</th>
<th>n</th>
<th>% (95% CI)</th>
<th>n</th>
<th>% (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route of exposure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ingestion</td>
<td>69</td>
<td>53 (44 to 61)</td>
<td>2</td>
<td>11 (2 to 36)</td>
</tr>
<tr>
<td>Insufflation</td>
<td>42</td>
<td>32 (24 to 41)</td>
<td>5</td>
<td>29 (11 to 54)</td>
</tr>
<tr>
<td>Parenteral</td>
<td>2</td>
<td>2 (0 to 6)</td>
<td>0</td>
<td>0 (0 to 22)</td>
</tr>
<tr>
<td>Other/multiple</td>
<td>2</td>
<td>2 (0 to 6)</td>
<td>2</td>
<td>11 (2 to 36)</td>
</tr>
<tr>
<td>Not known</td>
<td>16</td>
<td>12 (5 to 16)</td>
<td>9</td>
<td>50 (26 to 73)</td>
</tr>
<tr>
<td>Persistence of symptoms after exposure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;24 h</td>
<td>59</td>
<td>45 (36 to 54)</td>
<td>4</td>
<td>22 (7 to 48)</td>
</tr>
<tr>
<td>&gt;48 h</td>
<td>39</td>
<td>30 (22 to 38)</td>
<td>1</td>
<td>6 (3 to 29)</td>
</tr>
</tbody>
</table>
Allowing for these limitations, however, it is apparent that structured data collected by the NPIS may be of use in identifying trends in poisoning and in establishing toxicidromes for new drugs of abuse. Enquiries relating to methedrone in particular have become commonplace in the UK, reflecting a substantial workload for healthcare professionals, especially those working in emergency departments. This may be partly offset by reductions in presentations associated with other stimulants such as MDMA and cocaine, although it is too early to draw reliable conclusions.

Most methedrone exposures are not associated with severe toxicity although, as predicted from its amphetamine-like chemical structure, sympathomimetic effects are common and have been described previously in one case of confirmed methedrone exposure and in a series of exposed people attending an emergency department in London. A similar pattern of common effects was associated with other stimulants such as MDMA for healthcare professionals, especially those working in emergency departments. This may be partly offset by reductions in emergency departments. This may be partly offset by reductions in

The occurrence of severe features including hallucinations, chest pains and convulsions is of particular concern. The reported episode of apparent myocardial infarction is of interest; it is not possible to demonstrate causality from this single report, but an increased risk of myocardial infarction has been reported in users of khat. Other effects such as confusion, fever or myoclonus may reflect serotoninergic actions of the drug.

One patient in this series died having experienced cardiac arrest, apparently in the context of methedrone use, but subsequent investigation suggested that methedrone was not responsible. Deaths have previously been reported in methedrone users and in some cases toxicological confirmation of the presence of methedrone is available, although this does not prove that death was caused by methedrone exposure.

It is of interest that clinical features, including severe effects, sometimes appear to persist for (or occur) more than 24 h after the most recent reported exposure. The explanation for this is unclear; elimination of other cathinones appears rapid, with elimination half-lives in humans reported as 1.5–5 h for cathine and 5.2 h for cathinone. Pharmacokinetic information is not currently available for methedrone. For amphetamines, repetitive use has been reported to increase the apparent half-life and duration of effect.

NPIS data are not helpful for predicting the longer term toxic effects of methedrone, but available data for other cathinones are not reassuring. Use of Khat has been associated with an increased risk of psychosis while methcathinone (ephedrine), a dopamine and serotonin transporter substrate, reduces frontal concentrations of dopamine and serotonin and has toxic actions against dopaminergic and serotonergic neurons. A Parkinsonian syndrome has been reported in the intravenous use of methcathinone synthesised from pseudophedrine using potassium permanganate, although this appears to result from chronic manganese toxicity rather than as a direct neurotoxic effect of the cathinone.

It remains to be seen what effects recent changes in legal status may have on the pattern of presentations associated with the toxicity of methedrone and other cathinones. In the meantime, health professionals, especially those working in emergency departments and drug rehabilitation services, should be aware of methedrone and its acute toxic effects.

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Contributors All authors were involved in the design of the study and approved the final manuscript. DJ, RA, RS, GC and DJL obtained and analysed the data. SHLT and JPT drafted the manuscript. SHLT acts as guarantor.

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REFERENCES


