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TOXICOLOGY OBSERVATION

Recreational Use of Mephedrone (4-Methylmethcathinone, 4-MMC) with Associated Sympathomimetic Toxicity

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Abstract
Introduction Cathinone is a pharmacologically active alkaloid that can be extracted from the leaves of the khat plant (*Catha edulis*). There are synthetic derivatives of cathinone entering the recreational drug market, including mephedrone (4-methylmethcathinone, 4-MMC). There are discrepancies in the legal status of both the khat plant and its extracted alkaloids between the UK and the USA.
Case Report A 22-year-old man purchased 4 g of mephedrone powder over the Internet from a chemical supplier based in China. He initially ingested 200 mg of the mephedrone orally, with no perceived clinical effects, and thereafter injected the remaining 3.8 g intramuscularly into his thighs. Shortly after the injection, he developed palpitations, "blurred tunnel vision," chest pressure, and sweating and felt generally unwell; he presented to hospital with continuing features of sympathomimetic toxicity. His symptoms settled over the next 4 h after a single dose of oral lorazepam. Qualitative analysis of the urine and serum sample was undertaken using gas chromatography with mass spectrometric (GC/MS) detection, both positive for the presence of 4-methylmethcathinone. Quantitative analysis of the serum sample was undertaken by liquid chromatography with tandem mass spectrometric detection; the estimated mephedrone concentration was 0.15 mg/l. Routine toxicological analysis of the serum and urine specimens using a broad GC/MS toxicology screen did not detect any other drugs or alcohol.

Previous Presentations This case report was presented at the North American Congress of Clinical Toxicology, in San Antonio, TX, USA in September 2009.

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Discussion This is the first case of isolated 4-MMC toxicity, with confirmatory analytical findings. It is important that clinical toxicologists and emergency physicians work together to ensure a better understanding of the toxicity of novel/emerging drugs such as 4-MMC.

Keywords Mephedrone · 4-Methylmethcathinone · Recreational drugs · Toxicological screening · Khat

Introduction

Cathinone is a pharmacologically active alkaloid that can be extracted from the leaves of the khat plant (*Catha edulis*, also known as quat or chat) [1, 2]. The plant is an evergreen shrub that is found predominately in Africa and the Middle East, the leaves of which are chewed by people from those areas for their stimulant properties [3]. The fresh leaves contain cathinone, but this is rapidly degraded and broken down into cathine [4, 5]. These compounds are close chemical relatives of synthetic stimulants such as amphetamine or methcathinone. The pharmacological activity of the leaves is thought to relate to cathinone, rather than cathine and, therefore, their activity lasts for only a few days after they have been harvested [4, 5]. Cathinone is thought to produce its desired stimulatory effects through the release of presynaptic catecholamines [4, 6, 7]. We are aware that synthetic derivatives of cathinone are entering the recreational drug market, including mephedrone (4-methylmethcathinone, 4-MMC), ethcathinone, and 3-fluoromethcathinone, from analyses of samples from drug amnesty bins that we have undertaken.

There have been no cases of confirmed toxicity associated with recreational use of mephedrone previously reported. We report here the first case of recreational use of mephedrone that resulted in sympathomimetic toxicity, with confirmatory toxicological analyses.

Case Report

A 22-year-old man purchased a total of 4 g of mephedrone powder over the Internet from a chemical supplier based in China. He ingested 200 mg of the purchased mephedrone orally, with no perceived clinical effects, or the desired "high." Therefore, after a "few hours," he decided to inject the remaining mephedrone to see if this would lead to the desired effects. He diluted the remaining 3.8 g of mephedrone in sterile water that had been purchased from a local pharmacy. The diluted solution was then injected intramuscularly, in multiple sites in both his thighs. Shortly after injection of the mephedrone, he developed palpitations, "blurred tunnel vision," chest pressure, sweating, and a feeling of being generally unwell. He also developed a fixed belief that he had mercury poisoning. This belief arose from his investigations on the Internet including information which he had found that mephedrone can be contaminated with mercury due to its use in the synthesis of mephedrone.

He was reviewed by the clinical toxicology service on presentation to the emergency department. He was noted to be anxious and agitated, with continuing features of sympathomimetic toxicity (heart rate of 105 beats per minute, blood pressure of 177/111 mmHg, dilated pupils of 7 mm). There was no evidence of diaphoresis. He was apyrexial (36.2°C) and had oxygen saturations of 98% on room air with a respiratory rate of 18 breaths per minute. Apart from the dilated pupils, the remainder of his neurological examination was normal, and in particular there was no evidence of hypertonia, hyperreflexia, and inducible/spontaneous clonus or bruxism, and his visual field examination was normal. There was no erythema or swelling around the injection sites in his thighs.

His admission electrocardiogram showed a sinus tachycardia with normal QTc and QRS durations; initial laboratory biochemical tests were: potassium 3.8 mmol/l (3.8 mEq/l), creatinine 97 μmol/l (1.09 mg/dl), and glucose 5.8 mmol/l (105.5 mg/dl). An initial venous blood gas showed no evidence of a significant acid–base disturbance (pH7.45, $PaCO_2$ 4.85 kPa (36.5 mmHg), bicarbonate 24.5 mmol/l (24.5 mEq/l), base excess −0.8 mmol/l, lactate 1.0 mEq/l (9.0 mg/dl)).

In view of his agitation and other ongoing sympathomimetic features, he was treated with 1 mg lorazepam orally and admitted for observation. Over the course of the next 4 h, his symptoms of agitation and anxiety settled, along with his clinical markers of sympathomimetic toxicity (heart rate of 90 bpm and blood pressure of 110/67 mmHg). A blood mercury concentration was measured as 9 nmol/l (normal range <50 nmol/l), and he was reassured that there was no evidence of mercury toxicity. He was therefore discharged home 6 h after presentation to the emergency department.

Toxicological Screening

Informed consent was obtained from the patient for toxicological analysis of serum and urine samples collected on admission, when the patient was clinically symptomatic as described above. Screening methods and techniques were developed for eight methcathinone-related compounds, including mephedrone, by the Analytical Unit at St. George's, University of London. Derivatives of both cathinone and methcathinone were synthesized in-house, by Kingston University, to act as secondary standards in the

analyses, and their identity was established by nuclear magnetic resonance (NMR). ^{1}H NMR did not show the presence of any other materials. Qualitative analysis of the urine and serum sample was undertaken using gas chromatography with mass spectrometric (GC/MS) detection. The urine and serum samples were both positive for the presence of 4-methylmethcathinone (mephedrone). Quantitative analysis of the serum sample was undertaken by liquid chromatography with tandem mass spectrometric detection. Using our synthesized methcathinone, as there are no certified reference standards, the serum concentration of mephedrone was estimated to be 0.15 mg/l

Routine toxicological analysis of the serum and urine specimens using a broad GC/MS toxicology screen did not detect any other drugs or alcohol in either the serum or urine samples.

Discussion

We have reported here the first case of mephedrone toxicity with sympathomimetic toxicity following recreational use. Subsequent toxicological analysis of serum and urine samples obtained following presentation to the emergency department confirmed that this was isolated mephedrone toxicity.

Mephedrone is a synthetic chemical which is chemically and structurally similar to cathinone, which can be extracted from the khat (*C. edulis*) plant. Mephedrone, like other derivatives of cathinone, is currently not controlled under the relevant drugs legislation in the UK and the USA.

There have been no previously published cases of mephedrone toxicity, with or without confirmatory analytical findings in the medical literature. There has been a fatality reported in the "lay press," which was attributed to the use of mephedrone and cannabis [8]. No toxicological findings from this fatality have been published in the medical literature to confirm that the death was a direct result of the use of mephedrone. There have been variable user reports on the Internet concerning both the desirable and unwanted effects of mephedrone [9-12]. These reports are submitted by "users" of mephedrone to Erowid, an online library containing information about psychoactive drugs, plants, and chemicals, and often information on sites such as Erowid may be the first information available to clinicians before publications appear in the medical literature. These users have either insufflated or ingested mephedrone powder; there have been no previous reports of parenteral use of mephedrone. In general, mephedrone is reported to have a stimulant effect, although unlike other stimulant drugs, some users report that it does not have an associated euphoric effect [10]. Commonly reported unwanted effects following use of mephedrone include tachycardia, nasal irritation secondary to insufflation of the powder, restlessness, and bruxism. One user reported symptoms suggestive of peripheral vasoconstriction and severe anxiety/agitation, although they did not seek medical attention to determine the cause of their symptoms [12].

There have been no reported cases of toxicity associated with the other cathinone derivatives ethcathinone and 3-fluoromethcathinone in the medical literature. There have, however, been reports of acute toxicity associated with cathinone and methcathinone [13-15]. In a follow-up survey of 34 individuals initially discussed with a poisons center in Israel following use of "Hagigat" capsules, which contain cathinone, common unwanted effects included gastrointestinal (nausea, vomiting, diarrhea), cardiovascular (tachycardia, hypertension), neurological (headache, restlessness, anxiety), and respiratory (dyspnea) [13]. There have been numerous reports of "parkinsonism" like neurological toxicity developing following intravenous injection of "Russian Cocktail" across Russia and a number of former Eastern European countries [16-22]. These individuals had been injecting methcathinone, and initially it was thought that their symptoms directly related to this. However, on further investigation and detailed toxicological analysis, it was found that the solutions being injected had high concentrations of manganese and that, in fact, the extrapyramidal features were related to manganese toxicity [16-22].

We have previously reported the benefits of proactive ad hoc toxicological screening in individuals who self-report the use of "novel" drugs [23-26]. Detailed toxicological screening in these cases has established that the presentations were related to the use of a novel drug and contribute to the understanding of the potential toxicity of novel drugs as they enter the recreational drug scene. The case reported here, the first confirmed toxicity associated with a synthetic cathinone derivative, further supports that clinical toxicologists and emergency physicians should be vigilant to identify these cases, undertake detailed toxicological screening, and contribute to our understanding on the toxicity associated with novel recreational drugs.

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

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