Correspondence case report

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The identification and chemical characterization of a new arylcyclohexylamine, methoxetamine, using a novel Emergency Department toxicosurveillance tool

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Introduction and case report

The Emergency Department is frequently the first port of call for patients suffering from recreational drug overdose, alongside pre-hospital and other emergency services. Many drugs are familiar to the seasoned practitioner, but the fluctuant and dynamic nature of both the licit and illicit recreational drugs market is such that there are always new products emerging. Manufacturers, eager to avoid prosecution where possible, have put some effort into developing the 'legal high market', using untried and untested compounds bearing labels such as 'research chemicals' to bypass the legal ramifications of selling drugs to consumers.[1]

One such recently described group of so-called legal highs are the substituted cathinones, of which mephedrone is the best known.[2] We believe that drugs from the arylcyclohexylamine class are becoming the next class of legal highs to significantly spread through the drug-using community, and that both clinicians and analytical chemists should be aware of their existence and effects.

A 35-year-old man presented to the Emergency Department at Nevill Hall, Abergavenny (South Wales) in early 2011, having collapsed at his home. He was initially unresponsive on ambulance arrival, and was noted to be bleeding from his left nostril, following insufflation of a white powder (although there was no evidence of further nasal irritation resulting from insufflation). A small empty package was found with the patient, which was labelled with the chemical structure of the compound and the word 'methoxyphenyl-2-(ethylamine) cyclo-hexanone'.

The patient was initially incoherent in his general manner and communication with Emergency Department staff, but returned to a GCS (Glasgow Coma Scale) of 14 over 20 min, and a GCS of 15 over 90 min. He was hypertensive (blood pressure = 167/110 mmHg), but not tachycardic (with heart rate and temperature in the normal range), and he had bilateral pupillary mydriasis. Neurological examination was normal, with no focal neurological signs. He described being in contact with both heaven and hell and the spirit of his dead father. His behaviour was ecstatic, but otherwise good-natured. He appeared to be confused about the origins of sounds and colours in his proximity, but denied frank hallucinations.

On further enquiry, he was identified as having had previous mental health issues, and was known to have been treated for bipolar disorder using lithium, but had been non-compliant. He was managed conservatively in the Emergency Department, with cardiac monitoring (electrocardiograms revealed normal sinus rhythm), and admission blood tests (including full blood count, Na/K/urea/electrolyte levels and liver function tests) revealing no abnormalities.

As his condition improved over a period of around 90 min, he freely admitted to consuming the compound that had been contained in the empty package, which he described as 'methoxetamine', a drug unfamiliar to the treating doctors at the time of presentation in early 2011. He had purchased this online (1 g for £35.00 - at the time of writing, USD $55). He had insufflated 25 mg initially, a further 25 mg half an hour later, and pleased with the initial effects, the remains of the package (950 mg). He consented to allowing the residual contents of the labelled package found on his person to be analyzed, and it was forwarded for further analysis. Despite the large quantity of product ingested, there appeared to be no short-term sequelae to his overdose. He was admitted to hospital for observation and, given his prior history of bipolar disorder and delusional presentation on admission, was sent for further evaluation by psychiatric services. The patient was discharged several days later.

Materials and methods

Gas chromatography–mass spectrometry (GC-MS)

The analyses were carried out on a Varian 4000 series gas chromatograph equipped with a Combi-Pal autosampler and a series 4000 ion-trap mass selective detector. The gas chromatograph was equipped with a CP-Sil 8 CB (30 m × 0.25 mm i.d., 0.25 μm film thickness) capillary column from Varian. Helium

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was delivered at 1 ml/min to the analytical column, which was ramped from 100 °C to 280 °C at a rate of 20 °C/min and held at the final temperature for 1 min. The injector port was maintained at 250 °C and operated in splitless mode. Mass spectra were acquired in electron impact (EI) mode (scan range 160–250), and the sum of the 190, 219, and 248 ions were selected for the purposes of quantitation.

Nuclear magnet resonance (NMR) spectroscopy

A small quantity of drug sample (4 mg) recovered from the patient was dissolved in 0.5 ml of deuterated-methanol (d_4-MeOH, 99.9% D; Goss Chemicals, U.K). ^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded on a Bruker AVANCE 500 MHz instrument; chemical shift values are presented in ppm and coupling constants (*J* values) are in Hz. Multiplet peaks on the NMR spectrum are labelled as: s = singlet, d = doublet; t = triplet, q = quartet.

Results

A quantity of 4 mg of the product was dissolved in methanol (4 ml), which in turn was diluted 1:100 with ethyl acetate prior to GC-MS analysis. Methoxetamine appeared with a retention time of 7.35 min (Figure 1) and the mass spectra derived from the sample (Figure 1) were as would be predicted from the drug's formula. Because no standards were available for this compound at the time of study, it was further analyzed using ^{1}H and ^{13}C NMR spectroscopy, definitively confirming the chemical structure of the product. The NMR data was found to entirely consistent with the chemical structure of pure methoxetamine as predicted based on the GC-MS analysis and the label on the bottle of the patient's drug sample. ^{1}H and ^{13}C NMR (DEPT) spectra for methoxetamine in d_4-MeOH are presented in Figures 2 and 3, respectively. The compound numbering scheme is as presented in the methoxetamine structure of Figure 4.

Methoxetamine NMR data

Details of the ^{1}H and ^{13}C NMR data for the sample recovered from the overdose patient are presented below (where Ar = aryl, and compound numbering scheme is as presented in Figure 4).

^{1}H NMR (500 MHz, d_4-MeOH): δ 7.53 (1 H, t, J = 8 Hz, H-5′), 7.15 (1 H, dd, J = 8, 2 Hz, ArH), 7.05 (1 H, dd, J = 8, 2 Hz, ArH), 6.98 (1 H, t, J = 2 Hz, H-2′), 3.87 (3 H, s, CH_3O), 3.24 (1 H, dt, J = 11, 3 Hz, H-6), 2.85 (1 H, td, J = 7, 5 Hz, H-6), 2.51 (2 H, q, J = 7 Hz, $C\underline{H}_2CH_3$), 2.51 (1 H, m, H-3), 2.11 (1 H, m, H-3), 2.01 (2 H, m, CH_2), 1.82 (2 H, m, CH_2), 1.23 (3 H, t, J = 7 Hz, $C\underline{H}_3CH_2$).

^{13}C NMR (125 MHz, d_4-MeOH): δ 207.2 (C = O), 162.4 (C-1′), 132.9 (C-3′), 132.4 (C-5′), 121.3 (ArCH), 116.7 (ArCH), 115.5 (ArCH), 73.2 (C-2), 56.1 (CH_3O), 40.2 (CH_2), 38.4 (CH_2), 33.7 (CH_2), 28.6 (CH_2), 22.9 (CH_2), 11.6 (CH_3CH_2).

Discussion

Methoxetamine (2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone) is an arylcyclohexylamine analogue of the potent dissociative anaesthetic ketamine (Figure 4).[3] Structurally, methoxetamine is also related to the dissociative drug phencyclidine ((1-phenylcyclohexyl) piperidine, PCP, 'angel dust') and the veterinary anaesthetic tiletamine (Figure 4). Although these cyclohexanone-based drugs contain a chiral centre, they are normally prepared and used (and abused) in their racemic form. Literature abounds on morbidity and mortality associated with recreational PCP[4,5] and ketamine,[6] including information on the recently described ketamine vesicopathy.[7] Several overdoses from tiletamine have been described.[8,9]

At the time of patient presentation in early 2011, the authors could find no reference in the medical or forensic literature to date on the medical effects of methoxetamine or its two closely related compounds 2-(3-methoxyphenyl)-2-(ethylamino) cyclohexane, (3-MeO-PCE, methoxieticyclidine) and 3-methoxyphencyclidine (3-MeO-PCP). This case report represents an early description of a case study of methoxetamine overdose in humans in the forensic or medical literature, and is novel in its

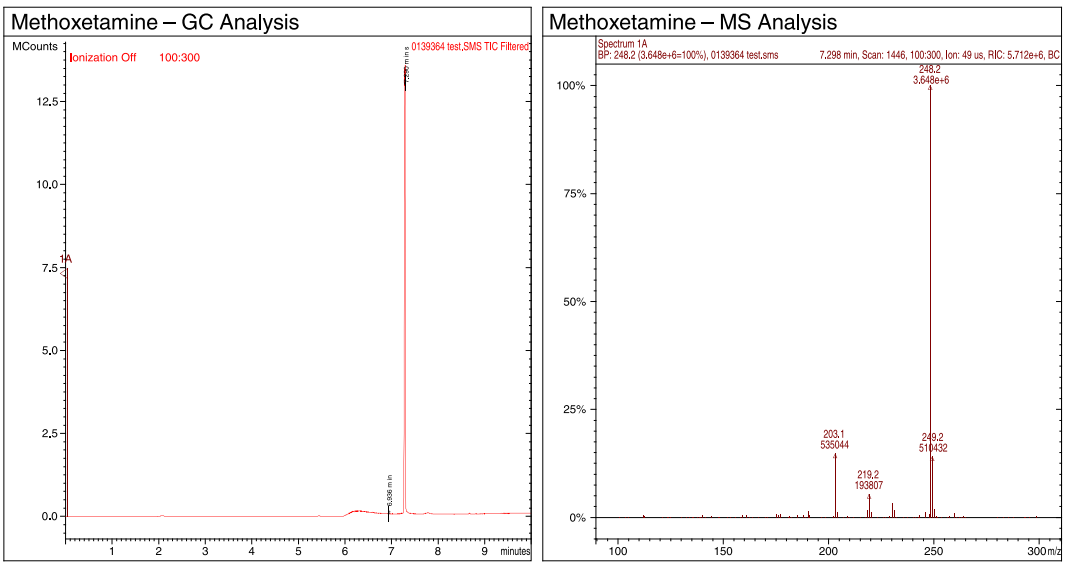

Figure 1. GC and MS analysis of methoxetamine (from patient sample).

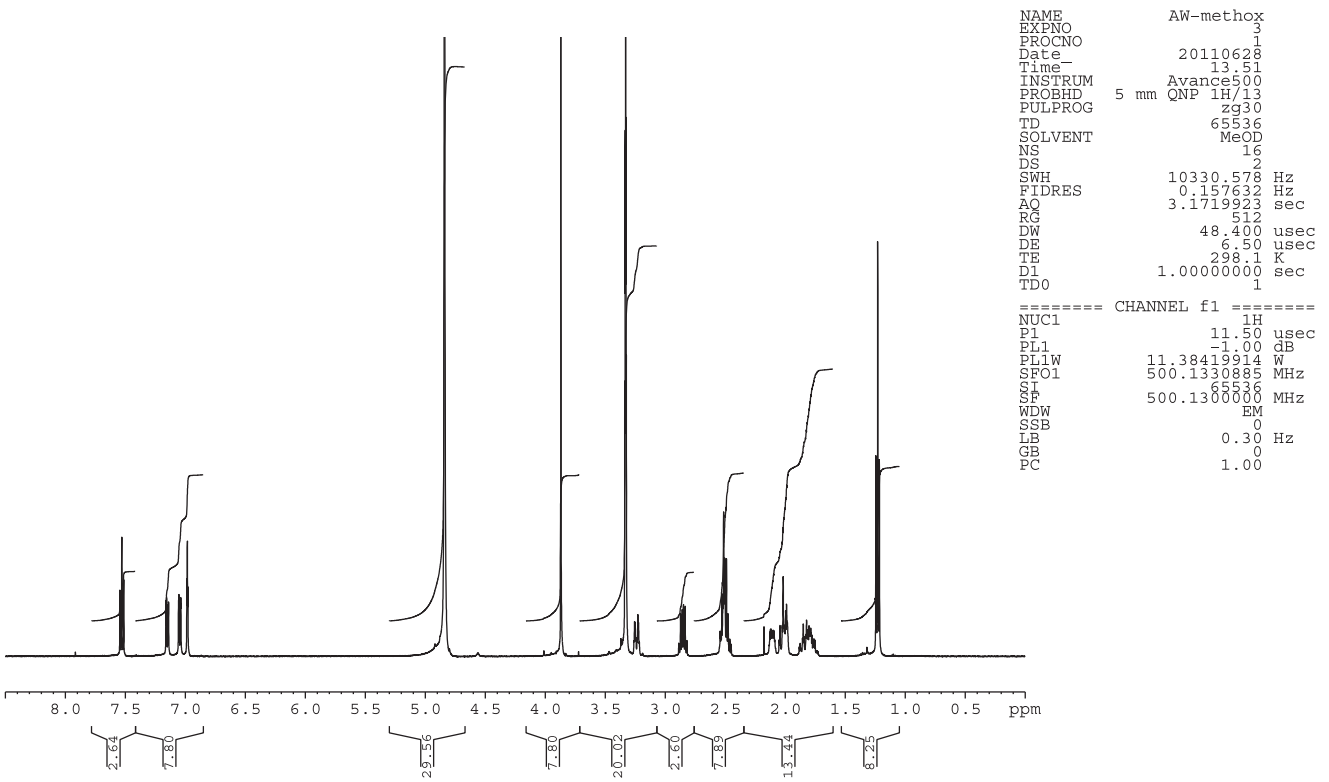

Figure 2. ^{1}H NMR spectrum of methoxetamine (from patient sample).

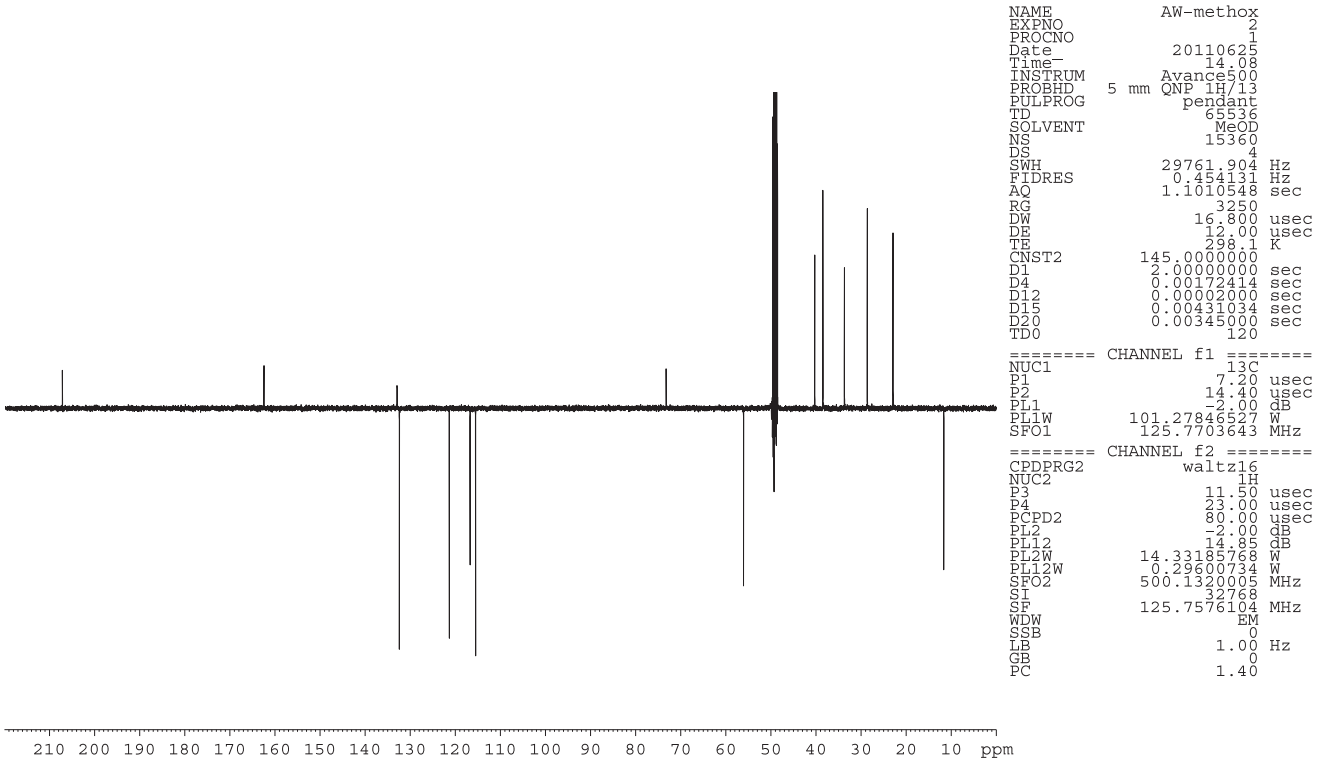

Figure 3. ^{13}C NMR spectrum of methoxetamine (from patient sample).

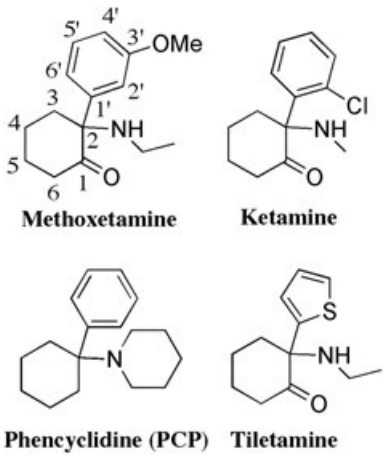

Figure 4. Chemical structures of methoxetamine and related psychoactive drugs.

use and report of rigorous chemical and analytical characterisation of the drug sample using NMR spectroscopy and GC-MS.

During the past year or so, reports have appeared in the literature concerning increasing use and consequent toxicological properties of methoxetamine.[3,10,11] In the UK, recent reports of deaths linked to use of methoxetamine[12] (also known as MXE or mexxy) have culminated in the drug being made illegal for up to 12 months from March 2012, using a UK Temporary Class Drug Order (TCDO) for the first time.[13] Unlike several recent iterations of sympathomimetic agents on the market, methoxetamine further represents the first dissociative hallucinogen agent to emerge since ketamine and PCP. In recreational drug terms, this represents the toxicological equivalent of a significant antigenic 'shift', compared to the 'drift' of the various sympathomimetics of the last decade.

In our patient, methoxetamine clearly appeared to have had a dissociative effect like ketamine, as well as an entheogenic, even euphoric element. It has been speculated that increased potency is conferred on methoxetamine as compared to ketamine as a result of the replacement of the N-methyl with an N-ethyl group, and that the substitution of a 2-chloro to a 3-methoxy side chain makes methoxetamine longer lasting, less analgesic and anesthetising than ketamine.[11] Consumer websites suggest that for nasal insufflation, a common dose is between 20 and 50 mg.[14] Our patient therefore appears to have survived an overdose more than an order of magnitude greater than the effective dose required with very few ill effects. Initial effects are alleged to start at ~10 min, post-insufflation, with a peak of desirable effects beginning at 20–25 min, and lasting 1.5–2 h.[14] The alleged designer of methoxetamine has been interviewed for a popular culture magazine[15] and has suggested that large quantities of these products are manufactured in China.

The appetite for psychostimulant drugs by a wide demographic of the British population has been described elsewhere as 'voracious',[16] and shows no signs of abating in the face of current legislative policy. Emergency Departments are uniquely placed to identify harm caused by novel compounds before they become entrenched in the mainstream repertoire of drug use. Novel strategies, such as the use of amnesty bins to allow the submission of potentially undescribed compounds as they emerge on the illicit market,[17] as well as *ad hoc* toxicological assessment of patients when a new product is suspected[18] will identify new drugs faster than any other system described to date. The Emergency Department can also collect de-identified data regarding location of overdoses, mapping the use of novel compounds as they spread using GIS data management programs.

Methoxetamine appears to a potent dissociative psychostimulant, which is widely available for online purchase. The quantity ingested by our patient without life-threatening physiological compromise appears to be an order of magnitude greater than that recommended as an effective dose. It may however potentially pose significant risk to the consumer through behavioural change and loss of consciousness.

The Emergency Department can further serve to help moderate some of the more hysterical claims of the tabloid press by providing factual evidence regarding the harms of new drugs as they emerge. Published work in this field has called for more informed accountable reporting on drugs across all of the media, and we strongly support this approach.[19] The publicity given to these products, particularly by the tabloid press, has little or no health benefit in dissuading consumers.

Beyond the nascent and evolving knowledge of the toxicology of these novel products lie bigger questions, questions that Emergency Departments can play a role in answering. The rampant success of similarly marketed drugs (in commercial terms, for the suppliers) will not only guarantee the popularity of methoxetamine and related products themselves, but more generally the manner (i.e. legal online websites) in which they have been marketed. The marketing of these products is now a sophisticated operation, highly targeted to a specific user group who have a distorted concept of risk. Strategies to minimise harm must evolve in parallel, focussing on the gathering and dissemination of accurate information to both consumer and those treating the consumer.

The Emergency Medicine community could naturally assume a major role in this endeavour and should therefore be actively involved from the outset in the planning of such strategies. *Ad hoc* analysis of products arriving at the Emergency Department has been described, and more recently, the analysis of multiple products from a single Emergency Department has been reported.[20] The Welsh Emergency Department Novel Substances (WEDINOS*) group has been established to foster closer ties between emergency clinicians and their analytical chemist counterparts in the combined endeavour of identifying novel products at national level, for epidemiological purposes. By having set protocols in place to identify novel products as they present with patients to the Emergency Department, we can maximize the rate at which these compounds, in this rapidly mutating market, can be identified. Ensuring patient anonymity encourages their participation in the programme, and the feedback that we have received has been universally positive. The association of these products with acute hospital presentations presents *de facto* and intuitive evidence of their potential for harm, and is far more persuasive a disincentive for further consumption for this tech-savvy generation than any morality-based campaign. Having this 'hot' information to hand permits easier dialogue with further consumers.

In summary, we believe that countries in which the public health benefits of this knowledge are seen to outweigh the benefits of criminal prosecution of individuals for low quantity possession could benefit from adopting a similar model.

**wedi nos* is Welsh for 'after dark'

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