

Multiple Fatalities Involving a New Designer Drug: *Para*-Methyl-4-Methylaminorex

In recent years, the pace at which new psychoactive substances (NPS) have emerged has accelerated considerably. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) reported that between 2005 and 2011, 164 NPS were formally notified through the early warning system. While 49 NPS were notified in 2011 alone (1), a further increase of 73 NPS has been observed for 2012 (2). Many of these substances are sold in so-called head shops or over the internet and are often described as “not for human consumption” to avoid regulatory difficulties. The commercial availability of these substances may differ between countries but appears to be influenced by their control status, which means that there may be a tendency to change the product catalog of available substances by introducing new analogs that may not be captured by legislative control.

The toxicity of these new substances is often poorly understood, although many of the compounds appear to have psychoactive and psychostimulant properties in humans. However, fatal toxicity has been attributed to many of these compounds as well, either with or without the presence of other drugs (3). A cluster of deaths in Northern Ireland occurred during 2013 and several of these were associated with the police seizure of tablet items (“Speckled Cherry” and “Speckled Cross” motifs).

The analysis of both tablet types revealed the presence of a new designer drug which was characterized as *para*-methyl-4-methylaminorex (4,4'-DMAR) which appears to be known, among other names, as “Serotoni” (4). The presence of two chiral centers gives rise to two diastereomeric *cis*- and *trans*-racemates, and further work is required to unambiguously identify the species identified in these cases. Although 4-methylaminorex and aminorex are listed as controlled substances in the UK legislation, the *para*-methyl derivative is not subject to control at this time. 4,4'-DMAR derives from a range of aminorex analogs that have been explored in the 1960s as potential appetite suppressants (5), which have been occasionally considered as potential designer drugs (6). However, 4-methylaminorex (U4Euh) was perhaps one of the few analogs that have attracted some attention first in the 1980s (7–9).

The presence of 4,4'-DMAR was detected in toxicology samples submitted in a number of drug abuse deaths; some of which were directly associated with the tablet seizures. To date, the drug has been detected (in blood/urine/gastric contents) in a total of 18 fatal cases in Northern Ireland. In all of these cases at least one other drug was also detected.

Excluding two of the cases, where the drug concentrations were very low (<0.02 mg/L), post mortem concentrations of 4,4'-DMAR, ranged from 0.20 to 3.75 mg/L (median 1.18 mg/L).

The presence of 4,4'-DMAR was first notified to the EMCDDA in December 2012 (2) but to the best of the authors' knowledge, there have been no formally published case reports on fatal cases associated with this drug. However, there are indications that this drug may have also been involved in eight recent fatalities in another European country (10).

The purpose of this communication is to draw attention to this drug within the toxicology community and include brief analytical information and toxicological findings. A more detailed case report will be the subject of future publication and will include

pathological findings, further case information and likely toxicological impact of the drug.

Tablet Seizures

So far, two tablet types have been identified which have been found to contain the drug; both were speckled brown in color and bore either a “cherry” or a “cross” imprint. Approximate dimensions were 9.0 × 3.8 mm (speckled cherry) and 8.9 × 4.3 mm (speckled cross).

Toxicological Analysis

Although basic drug (un-derivatized) GC–MS screening proved relatively insensitive, satisfactory results were obtained with the implementation of ultra/high-performance liquid chromatography with diode array detector (U/HPLC-DAD) and LC–MS (both nominal mass LC–MS and high-resolution U/HPLC–MS). Cross-reactivity with common immunoassay screening kits has not been determined. Suspected 4,4'-DMAR (not certified) was donated by Scientific Supplies Ltd. (London, UK), and structural characterization with regards to its *cis/trans* identity will be published in due course elsewhere. A stock solution of the drug was prepared at a concentration of 1 mg/mL in methanol and kept in the freezer. This stock solution was used to prepare working standard solutions in methanol.

High-resolution LC–MS

Initial identification in biological fluid was obtained using an Agilent 6540 QTOF-MS with subsequent screening of further cases carried out using an Orbitrap Exactive Plus instrument, based on a protonated accurate mass of m/z 191.1178. Case extracts were prepared from blood, urine and gastric contents by solid-phase extraction using Biotage ABN cartridges.

Liquid chromatography–mass spectrometry

Targeted quantitative analysis was carried out using an Agilent LC-MS/MSD Trap with an Agilent Zorbax SBC-18 column (150 × 2.1 mm, 3.5 μm). The column temperature was set at 40°C with elution based on a formic acid and methanol gradient. The parent mass targeted during analysis was m/z 190.6, which fragmented to give the product ion at m/z 147.5. Extracts were prepared from blood, urine and gastric contents by liquid–liquid extraction at pH 11 into *tert*-butyl methyl ether and reconstituted in methanol. The approximate limit of detection determined for 4,4'-DMAR was 0.001 mg/L.

High-performance liquid chromatography with diode array detector

A Thermo Dionex 3000 Ultimate HPLC-DAD system was used (200–595 nm) with a Phenomenex Synergi Fusion column (150 × 2.0 mm, 4 μm). The column temperature was set at

30°C with elution based on a triethylammonium phosphate and acetonitrile gradient.

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