Use of Diethylone, a New Psychoactive Substance, Associated with Multi-system Toxicity: A Case Report of Two Patients

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Introduction

New Psychoactive Substances (NPS) is a term used to describe synthetic products that may also be referred to as “designer drugs”, “research chemicals”, or “internet drugs”. The three most common types of NPS in the United States are synthetic cannabinoids, synthetic cathinones, and designer opioids [1]. The World Drug Report of 2014 reported there has been a more than two-fold increase in the number of NPS on the global market between 2009 and 2013 [2]. A total of 644 NPS have been reported by The United Nations Office on Drugs and Crime Early Warning Advisory as of December 2015, which far surpasses the 234 controlled psychoactive substances listed [3].

We report the cases of two patients who reportedly used “Molly” and developed symptoms requiring Intensive Care Unit (ICU) admission for several days. Additional investigation identified diethylone in the substance the patients used, and several predicted diethylone metabolites in their sera. Clinical effects associated with diethylone use in humans have not previously been described in the medical literature.

Abstract

Introduction: New Psychoactive Substances (NPS) is a term used to describe synthetic products that may also be referred to as “designer drugs”, “research chemicals”, or “internet drugs”. As new NPS continue to emerge, drug users are exposing themselves to new chemicals with unknown effects.

Case report: We report the cases of two patients who reportedly used “Molly” and developed multi-system toxicity requiring Intensive Care Unit (ICU) admission for several days. Both patients presented with altered mental status and during their hospital course manifested neuromuscular hyperactivity and hemodynamic lability. Both patients also had neuropsychiatric symptoms lasting for days after the critical phase of their hospital course. Laboratory investigation using liquid chromatography-quadrupole time-of-flight mass spectrometry identified diethylone in the substance the patients used, and several predicted diethylone metabolites in their sera.

Discussion: Clinical effects associated with diethylone use in humans have not previously been described in the medical literature. Our cases highlight diethylone as a new NPS that can be associated with severe and prolonged toxicity.

Case Report

Patient 1

A 44-year-old man was brought to the Emergency Department (ED) by his mother with altered mental status and during their hospital course manifested neuromuscular hyperactivity and hemodynamic lability. Both patients also had neuropsychiatric symptoms lasting for days after the critical phase of their hospital course. Laboratory investigation using liquid chromatography-quadrupole time-of-flight mass spectrometry identified diethylone in the substance the patients used, and several predicted diethylone metabolites in their sera.

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Like Patient 1, chromatography-quadrupole analysis showed a formula match to M13. Details of the analytical method used to analyze the samples are published elsewhere [4]. Neither patient’s sera contained a formula match to diethylone. This report summarizes the clinical effects observed in two patients who had used the new psychoactive substance diethylone. The presence of diethylone was confirmed in a sample of the drug the patients used, and predicted metabolites of diethylone were confirmed in the blood of both patients.

Diethylone (aka 5-BDDE; 3', 4'-methylenedioxy-N,N-diethylcathinone; and N-ethyl-diyhydromethamphetamine) by chemical structure is a substituted cathinone, and has been touted as a new designer stimulant [5]. An extensive search of both peer-reviewed and “gray” clinical literature was void of any mention of this substance in patients, reported human or animal exposures, or its effects (see supplemental material). Correspondence with the WHO’s Global Synthetics Monitoring: Analysis Reporting and Trends Programme also confirmed they had not received any report of diethylone through their Early Warning Advisory on New Psychoactive Substances system as of January 2017 [6].

A review of online drug user forums only yielded mention of a few experiences with diethylone. While most reported intranasal administration, some also ingested it. Reported effects included diaphoresis, euphoria, muscle twitching, jaw clenching, diarrhea and vomiting, and mydriasis. The duration of effect was between six and thirteen hours.

Diethylone is structurally similar to the cathinones methylethylone and ethylone, and therefore may be expected to cause similar clinical symptoms. While there are forensic studies showing detectable ethylone and methylethylone found at autopsy, very few reports in the literature describe clinical features following such drug use [7,8]. After methylethylone use patients have been reported to return to normal within 24 hours, whereas ethylone in animal studies produces a more prolonged stimulatory effect [9,10]. One patient with confirmed methylethylone use was reported to have palpitations, agitation, fear, tremor, vertigo, vomiting, paresthesias, and muscle twitching; she was discharged from the ED on the same day of presentation [11].

Diethylone peaked on day 5 at 442 units/L. After transfer to the floor the patient continued to have episodes of delirium and hallucinations that were treated with haloperidol. On day 11 the patient was determined to be back to his baseline, and was discharged home.

Patient 2
A 37-year-old woman presented to the ED via EMS for altered mental status; she was the girlfriend of Patient 1. She was somnolent, maintaining her airway, opened her eyes to verbal stimuli, localized to deep sternal rubs, but did not answer questions or follow commands.

During her hospital course, the patient’s condition worsened and she was intubated. She also developed neuromuscular findings (hyperreflexia and rigidity) and hemodynamic lability and was treated with cyproheptadine and supportive care. CPK peaked at 198 on day 4. Like Patient 1, after transfer to the floor she had episodes of delirium and delusions and was treated with haloperidol. She was discharged on day 12.

Analysis of substance and specimens
The son of Patient 2 brought in a sample of the “Molly,” a fine white crystalline powder identified as the substance used by both patients. This sample, as well as the initial blood and urine specimens collected at ED presentation from each patient, were sent to the Clinical Toxicology and Environmental Biomonitoring Laboratory at the University of California, San Francisco for analysis using liquid chromatography-quadrupole time-of-flight mass spectrometry. The drug sample was found to contain diethylone (330 mg/ g powder), with no detectable ethylone, methylone, MDMA, methamphetamine, or amphetamine; no other drugs or known NPS were detected in the sample. Neither patient’s sera contained a formula match to diethylone. Patient 1’s serum analysis showed a formula match to diethylone-predicted metabolites M6, M7, and M13 (Figure 2). Patient 2’s serum analysis showed a formula match to M13. Details of the analytical method used to analyze the samples are published elsewhere [4].

Discussion
This report summarizes the clinical effects observed in two patients who had used the new psychoactive substance diethylone. The presence of diethylone was confirmed in a sample of the drug the patients used, and predicted metabolites of diethylone were confirmed in the blood of both patients.

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Figure 1: Acquired MS/MS spectra of diethylone identified in the product.

Figure 2: Structural and chemical formulas of diethylone and its predicted metabolites.
Both case patients experienced prolonged neuropsychiatric symptoms (confusion, delusions and hallucinations) for several days. It is unclear whether diethylone use alone, use of other substances, or the treatments given during hospitalization explains this pattern. The delayed onset of rigidity, hyperreflexia and clonus observed in the patients following admission was unanticipated. The etiology of these observed neuromuscular findings is uncertain and could be related to the combination of numerous treatments the patients received (haloperidol, fentanyl, benzodiazepines, cyproheptadine, intubation, ICU admission) rather than solely due to diethylone itself.

It is not clear when the patients used diethylone prior to ED presentation. While diethylone itself was found in neither patient’s sera, this is not unexpected due to metabolic transformation. Instead, predicted metabolites of diethylone were found in both patients. The substance identified as the one both took was positively identified as diethylone by laboratory analysis.

Medical toxicologists are on the frontline caring for patients who are using NPS, and new compounds are likely going to continue to emerge as drug markets evolve to outpace legislation. Our cases highlight diethylone as a new NPS that can be associated with severe and prolonged toxicity.

References