

Unusually Prolonged Presentation of Designer Drug Encephalopathy Responsive to Steroids

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abstract

The availability and use of novel psychoactive substances has risen dramatically over the last decade. The unpredictability of their toxicity constitutes a real challenge. We report a case of an adolescent who developed prolonged encephalopathy after ingesting “Hot Molly,” which was found to contain the novel psychoactive substance, methylenedioxybenzylpiperazine when analyzed by high resolution mass spectrometry assay. This is the first case of human toxicity from methylenedioxybenzylpiperazine ingestion in the medical literature confirmed by body fluid analysis presenting with significant and prolonged encephalopathy. The prolonged course may be due to CYP2D6 inhibition from a combination of the methylenedioxyphenyl moiety and the patient’s ultrarapid metabolizer pharmacokinetics. The response to high dose corticosteroids suggests a possible inflammatory effect that warrants further investigation.

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Dr Albadareen drafted the initial manuscript; Drs Thornton, Heshmati, Gerona, and Lowry critically reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

www.pediatrics.org/cgi/doi/10.1542/peds.2015-0073

DOI: 10.1542/peds.2015-0073

Accepted for publication Apr 7, 2015

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

The availability and use of novel psychoactive substances (NPSs) has risen dramatically over the last decade.¹ The use of these substances is associated with multiple challenges including unpredictable and sometimes severe toxicity.² We report a case of an adolescent who developed prolonged encephalopathy after ingesting “Hot Molly,” which was found to contain the NPS, 1-(3,4-methylenedioxybenzyl) piperazine (MDBP) when analyzed by high resolution mass spectrometry assay.

CASE REPORT

A previously healthy 16-year-old boy presented to the emergency department with 1-day history of confusion, flight of ideas, flat affect, and perseveration. Physical examination and vital signs were unremarkable except for disorientation and confusion, with no other lateralizing neurologic signs. Initial workup including a head

computed tomography scan was unremarkable except for a urine drug immunoassay screen positive for tetrahydrocannabinol. Cerebrospinal fluid (CSF) analysis initially revealed 0 white blood cells, 0 red blood cells, 16 mg/dL proteins, and 91 mg/dL glucose and no evidence of bacteria on Gram staining with an opening pressure of 46 cm H₂O. After 3 days of admission for further evaluation, he developed increased somnolence and a generalized tonic clonic seizure with bowel and bladder incontinence. Postictally, he was noted to repetitively say, “Hot Molly.”

His mental status continued to fluctuate over the course of the following 5 days with significant confusion. On hospital day 10, he developed eye fluttering, fencing of the arms, and unresponsiveness suggestive of a partial complex seizure. He was started on valproic acid (750 mg twice daily) despite the lack of seizure activity on EEG.

Extensive workup to elucidate the cause of his encephalopathy, including 2 lumbar punctures (LPs), MRI/magnetic resonance angiography/magnetic resonance venography (MRV), and 2 EEGs, all were unremarkable. A positron emission tomographic scan done around the 10th day revealed diffusely decreased cortical uptake suggestive of encephalitis.

A trial of high dose intravenous methylprednisolone 1000 mg daily for 5 days was initiated for a presumed diagnosis of autoimmune encephalitis at the 10th day of his hospital stay. Concurrently, autoimmune (paraneoplastic) antibodies were ordered, and serum, urine, and CSF samples were sent for comprehensive toxicology analysis using liquid chromatography-quadrupole time-of-flight mass spectrometry (LC-QTOF/MS; Agilent LC1260- QTOF/MS 6550; Agilent, Santa Clara, CA). The consumed compound was not available for analysis.

Improvement in the patient's mental status was noted within 24 hours after initiation of the methylprednisolone. By hospital day 12, he was noted to be almost back to baseline except for minimal concentration problems. He was discharged from the hospital on a steroid taper for 3 weeks. No autoimmune (paraneoplastic) antibodies were detected in samples sent for analysis. LC-QTOF/MS analysis came back positive only for MDBP. Remarkably, 25 ng/mL of MDBP was detected in CSF obtained 8 days after initial presentation (Table 1). None of the CSF sample from the first LP collected on day 3 was available for this analysis.

TABLE 1 Sample Analysis Report Using LC-QTOF/MS

| Sample | Date | Time | MDBP, ng/mL |
|--------|-------|--------|-------------|
| Blood | Day 3 | 0800 h | 575 |
| Serum | Day 3 | 0800 h | 650 |
| Serum | Day 3 | 1000 h | 422 |
| Urine | Day 3 | 0755 h | 850 |
| CSF | Day 8 | 1225 h | 25 |

Briefly, serum samples were extracted by protein precipitation by using acetonitrile: methanol (95:5 v/v) while urine and CSF samples were diluted 5-, 10- and 100-fold before LC-QTOF/MS analysis. A 2.5- μ L aliquot of each extracted and diluted sample was analyzed in LC-QTOF/MS. Chromatography was run by gradient elution by using Agilent Poroshell 120 column (2.1 \times 100 mm, 2.7 μ m) maintained at 50°C. Full scan data on parent and fragment ions were acquired by using an electrospray ionization source run in both positive and negative polarity. Compound matches to a comprehensive drugs database consisting of 550 designer drugs, drugs of abuse, and prescription drugs were done by using the "Find By Formula" algorithm in Agilent MassHunter Qualitative Analysis software. Quantitative analysis of confirmed drug in each sample was done by isotope dilution method by using Agilent MassHunter Quantitative Analysis software for data analysis.

At the time of his 6-week follow-up appointment, the patient had fully returned to his baseline. Due to the apparent prolonged clearance of MDBP in this case, CYP2D6 genotyping was performed and the patient was found to be an ultrarapid metabolizer (CYP2D6 *2A/*2A).

DISCUSSION

MDBP is an NPS that belongs to the piperazine family of compounds. This family of compounds is unique for containing a heterocyclic 6-membered ring that has 2 nitrogen atoms at opposite positions. Multiple piperazine compounds are used as NPS. Benzylpiperazine is the most commonly encountered and is frequently sold as "Party Pills."³ There are no previous reports of MDBP use in the medical literature.

The piperazines are thought to have their toxic effects via a combination of monoamine release and reuptake

inhibition.⁴ There are no published data concerning the mechanism of action of MDBP.

Piperazines psychiatric effects are similar to those of sympathomimetics and include agitation, confusion, anxiety, depression, paranoia, and auditory hallucinations.⁵ Tachycardia and hypertension are commonly described.⁵ Higher levels of benzylpiperazine have been associated with seizures,⁶ the longest reported symptoms last up to 24 hours after ingestion.³ Treatment after piperazine ingestion is supportive.

There are no previous reports detailing the human toxicity of MDBP. In this case, it was associated most prominently with prolonged encephalopathy. This may be due to the structural similarity to methylenedioxymethamphetamine (MDMA). MDMA is known to promote serotonin and dopamine release from neurons.⁷ In addition, MDMA had been shown to promote release of norepinephrine.⁸ MDBP may have similar effects. The methylenedioxyphenyl (MDPh) moiety present in MDBP may also impact its toxicity. Experience with MDMA and other similar structures reveals that the MDPh moiety is a potent inhibitor of cytochrome P450 enzymes, specifically CYP2D6.^{9,10} This is the result of a reactive intermediate formed by the metabolism of the parent drug, and it causes permanent inactivation of the enzyme.¹¹ A number of cytochrome P450 enzymes are implicated in drug metabolism. CYP2D6 is the primary enzyme involved in the demethylenation of the methylenedioxy ring in MDMA, a metabolic reaction also observed in MDBP.¹² Resulting inhibition of CYP2D6 by MDBP may help explain the prolonged symptoms seen in this case.

Pharmacogenomics may have also played a role in the prolonged toxicity seen in this case. There is a high

degree of variability in the CYP2D6 gene.¹³ Based on the number of functional alleles, patients can be categorized as ultrarapid, extensive, intermediate, or poor metabolizers. Clinically, this can manifest as having different serum levels from what is expected relative to drug dosing, causing more adverse effects or less therapeutic effects depending on the metabolizer's polymorphism.^{14,15} This patient was found to be a CYP2D6 ultrarapid metabolizer, which may have resulted in increased rate of enzyme inhibition due to rapid metabolism of the parent drug thus prolonging the duration of action of MDBP.

It is notable that this patient's clinical condition began to improve upon initiation of intravenous methylprednisolone. This may have been coincidental or it is possible that MDPH containing substances induce neurotoxicity and/or inflammation, which may respond to the corticosteroids.¹⁶ However, this has not been described to date with MDMA or MDBP. Further research is warranted to investigate the possibility that high dose steroids may be of benefit in toxicity seen with MDBP and similar compounds.

CONCLUSIONS

We report the first case of human toxicity from MDBP ingestion in the medical literature confirmed by body fluid analysis presenting with significant and prolonged encephalopathy. Due to the patient's ultrarapid genotype, the prolonged course may be due to the profound CYP2D6 inhibition from the MDPH moiety. The response to high dose corticosteroids suggests a possible inflammatory effect that warrants further investigation.

ACKNOWLEDGMENT

We thank Dr Gary Gronseth for his review of the manuscript and continuous support.

ABBREVIATIONS

CSF: cerebrospinal fluid
 LC-QTOF/MS: liquid chromatography-quadrupole time-of-flight mass spectrometry
 MDBP: methylene-dioxybenzylpiperazine
 MDMA: methylene-dioxymethamphetamine
 MDPH: methylenedioxyphenyl
 NPS: novel psychoactive substance

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Pediatrics 2015;136:e246

DOI: 10.1542/peds.2015-0073 originally published online June 8, 2015;

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