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CASE REPORT

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Does Hyperthyroidism Increase Risk of Death Due to the Ingestion of Ecstasy?

ABSTRACT: Ecstasy (3,4-methylenedioxymethamphetamine, MDMA) is a psychoactive amphetamine derivative widely used for recreational purposes. Deaths caused by acute drug intoxication with MDMA are rare but can often involve a severe hyperthermic episode. The factors underlying the increased risk of some ecstasy users to a fatal drug reaction are not known. We present a case report of a 24-year-old woman who developed fatal hyperthermia with multi-organ complications following MDMA use and was found at autopsy to have diffuse thyroid hyperplasia (Graves' disease). An antemortem blood MDMA concentration of 0.68 mg/L was measured in a sample obtained on admission to hospital. Although a cause and effect cannot be established, as the thyroid hormone is a major regulator of thermogenesis, we suggest that hyperthyroidism predisposed the subject to ecstasy-induced hyperthermia and that a pre-existing defect affecting temperature status could be one factor in explaining some ecstasy intoxication deaths.

KEYWORDS: forensic science, forensic toxicology, ecstasy, 3,4-methylenedioxymethamphetamine, fatal, hyperthermia, hyperthyroidism, Graves' disease

Ecstasy (3,4-methylenedioxymethamphetamine, MDMA) is a widely used psychoactive amphetamine derivative that is used recreationally for its ability to cause euphoria and, reputedly, a state of heightened empathy and introspection (1). In addition, MDMA is currently being tested in a clinical trial for the treatment of posttraumatic stress disorder (2), and plans have been developed for the testing of the drug for treatment of anxiety in patients with advanced-stage cancer (3). Animal data show that ecstasy can cause release in the brain of the neurotransmitters serotonin and dopamine (1). In this regard, a postmortem brain investigation has disclosed severely decreased levels of serotonin in the brain of a chronic ecstasy user (4), a finding probably caused in part by excessive release and depletion of the neurotransmitter.

Deaths attributed solely to MDMA intoxication appear to be very infrequent relative to the estimated large number of individuals using the drug (5,6) and are often associated with a fatal hyperthermic reaction [i.e., "serotonin syndrome" (7)] with multiorgan failure (8). Fatal MDMA intoxication is idiosyncratic and the reasons why some ecstasy users are especially susceptible to the toxic effects of the drug are still unknown. This case report relates a pre-existing disturbance in thyroid status to an ecstasy-related fatality.

Case History

A 24-year-old woman, reportedly a "casual user of ecstasy" for approximately 1.5 years, developed difficulty breathing and profuse sweating at a nightclub after ingesting 1.5 tablets thought to contain ecstasy. She had a history of anemia and possible thyrotoxicosis. She was not known to use any other drugs with the exception of vitamins and an oral contraceptive. In the emergency department she was markedly hyperthermic (up to 41.5°C) with acute delirium and tachycardia and had a cardiopulmonary arrest. Cardiac function was regained, but she remained deeply unconscious with evidence of renal and hepatic failure before dying 2.5 days postadmission. Hematological testing revealed a hemoglobin level of 65 g/L (adult female reference range: 120–150 g/L). The results of the thyroid function tests, in hospital, are provided in Table 1.

Postmortem examination performed pursuant to a Coroner's warrant confirmed severe (postcardiopulmonary arrest) hypoxic–ischemic encephalopathy, which was associated with marked cerebral swelling and cerebellar tonsillar herniation (coning). Centrilobular hepatic necrosis (shock liver), acute renal tubular necrosis, focal myocardial necrosis, and marked pulmonary congestion were also noted. The thyroid gland was diffusely enlarged with a weight of 70 g (normal adult range: 15–20 g) and showed diffuse hyperplasia of the follicular epithelium and patchy lymphoid infiltrates on histologic examination. These pathologic findings in conjunction with the results of clinical thyroid function tests (see Table 1) support a diagnosis of primary hyperthyroidism (Graves' disease).

Analytical Methods

Toxicological analyses were performed on a hospital admission blood sample taken approximately 3–4 h after drug ingestion. MDMA and methamphetamine were detected during a gas chromatography (GC) and gas chromatography-mass spectrometry (GC/MS) drug screening procedure for chemically basic drugs (9) with confirmation/quantitation performed using GC with nitrogen–phosphorous detection. Screening for barbiturates, opiates (morphine, hydromorphone, codeine, hydrocodone, levorphanol), cocaine and its metabolites, and cannabinoid metabolites was conducted by direct enzyme-linked immunoassay (ELISA; Immunalysis Corporation, Pomona, CA). Blood and urine were analyzed for

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TABLE 1—*Results of antemortem thyroid function tests.*

	Sample 1 (29-h Post-MDMA ingestion)	Sample 2 (46-h Post-MDMA ingestion)	Reference range
Thyrotropin (TSH) (mIU/L)	0.01	0.04	0.50–5.00
Free thyroxine (FT4) (pmol/L)	41	31	10–25
Triiodothyronine (T3) (nmol/L)	2.8	2.9	1.3–2.7
T3 uptake	0.63	0.59	0.24–0.35
Free T3 index	1.76	1.71	0.35–0.78

ethanol and other volatiles using headspace gas chromatography with flame-ionization detection (10).

Results and Discussion

Comprehensive drug screening disclosed only MDMA (0.68 mg/L) and traces of methamphetamine (<0.063 mg/L) in the antemortem blood sample of this individual, which was collected 3–4 h postdrug exposure.

The extent of toxicity to MDMA is variable among individuals, and there is a significant overlap between blood concentrations observed in cases of apparent recreational use, toxicity, and fatal overdose. The blood MDMA concentration observed in this subject was within the range of MDMA levels previously measured in both fatal cases of ecstasy intoxication and among recreational users of the drug. For example, antemortem (hospital admission) serum, plasma, or blood MDMA concentrations ranging from 0.55 to 4.33 mg/L (mean: 1.84 mg/L) were measured in five ecstasy users who subsequently died of MDMA intoxication (11); however, plasma MDMA concentrations ranging up to 0.84 mg/L were observed among recreational users who did not experience significant toxicity and had reportedly ingested between one and seven tablets (containing unknown amounts of the drug) in a dance party setting (12). Even higher MDMA blood concentrations have been reported in other cases, including an individual who experienced tachycardia and hypertension but survived a plasma MDMA level of 7.7 mg/L (8). The wide range of blood concentrations associated with fatal MDMA intoxication illustrates the importance of other factors in the pathogenesis of ecstasy overdose.

It is likely that the ability of MDMA to increase body temperature in humans (13) is a critical factor responsible for those ecstasy fatalities that are associated with severe hyperthermia (8,14). Although the mechanism by which ecstasy can produce an increase in body temperature is still debated, activation of the sympathetic nervous system and the hypothalamic–pituitary–thyroid axis might be involved (15). In this regard, surgical removal of the thyroid/parathyroid glands in rats abolishes the ability of MDMA to cause hyperthermia, whereas treatment with thyroxine partially restores the hyperthermic response (16). More relevant are the recent observations that chronically hyperthyroid rats show, in comparison with euthyroid animals, a more marked increase in maximal temperature elevation and in lethality consequent to acute exposure of MDMA (17).

Among the limitations of our case report is the absence of retrospective data on the clinical thyroid status of the subject with respect to the extent of heat intolerance. Information as to the ambient temperature in the nightclub and the level of activity of the decedent following ingestion are also unknown. In addition, the possibility that methamphetamine, which was found in a nonquantifiable trace concentration in antemortem blood, might have been a factor in the development of the fatal hyperthermia, although considered unlikely, cannot be completely excluded.

It is possible that the abnormal thyroid status of the decedent in this case may have been unrelated to the fatal outcome of the ecstasy exposure. However, the thyroid hormone is a major regulator of thermogenesis (18), and heat intolerance can be associated with hyperthyroidism in humans (19); thus, the hyperthyroid condition could have disposed this individual to MDMA-precipitated hyperthermia, as is the case in the aforementioned animal model (17). In this regard, the final cause of death was ruled for this case to be multisystem failure due to ecstasy intoxication with thyroid hyperplasia listed as a significant condition.

The basis for the idiosyncratic susceptibility of a small minority of ecstasy users to fatal hyperthermia is probably multifactorial, with factors such as ambient room temperature, physical activity, and fluid intake being involved. In the present case, the decedent was reported to have used ecstasy casually over a period of 1.5 years before developing a fatal reaction. Although additional data supporting this association is required to establish a link between hyperthyroidism and MDMA toxicity in humans, users of ecstasy for recreational or proposed therapeutic purposes, emergency room physicians, and those involved in the investigation of ecstasy-related deaths should nevertheless be aware of this possible relationship.

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