The Agony of "Ecstasy": 3,4-Methylenedioxymethamphetamine ("Ecstasy") - Induced SIADH and Symptomatic Hyponatremia

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Abstract

3,4-Methylenedioxymethamphetamine (MDMA), popularly known as the illicit drug "Ecstasy" is an amphetamine derivative that has become widely abused throughout the U.S. and other industrialized nations. MDMA has an undeserved reputation as a "safe" drug among its users, but MDMA shares the toxicity profile of other amphetamines. Its use may result in lethal cardiovascular, hepatic, metabolic, or neurologic toxicity. The syndrome of inappropriate antidiuretic hormone release (SIADH) is a unique toxicity that may occur after isolated MDMA use. Although the phenomenon is well described in adults, reports of MDMA-induced SIADH and symptomatic hyponatremia in children are rare.

We describe a 15 year-old girl who experienced MDMA-induced SIADH with symptomatic hyponatremia. Toxicity of MDMA, in particular the pathophysiology and treatment of MDMA-induced hyponatremia will be discussed.

Key words: *Ecstasy, methylenedioxymethamphetamine, MDMA, SIADH, hyponatremia, intoxication, toxicity*

Introduction

3,4-Methylenedioxymethamphetamine (MDMA), popularly known as "Ecstasy", is an illicit drug of abuse that has undergone an explosive expansion in use in the past decade (1,2). Initially developed as an anorexiant diet agent, this drug was largely unused from 1920 until the 1960's, when its particular stimulant properties were discovered. The potent serotonergic action of MDMA gives users a euphoria and intense feeling of happiness, love, and empathy (3,4). The tendency of MDMA to create these emotions and facilitate the user discussing them prompted psychologists to believe this represented a new class of drug, termed "enactogens" (5,6). Since the 1980's, MDMA has been used as a mind-altering substance at parties and dance clubs, the common circumstances of use today (7). In 1985, after recognition of increasing public use of the drug and recognition that it is a health hazard that may result in fatality, MDMA was legislated as a DEA Schedule I substance, with high abuse potential and no legitimate medical use. In the last decade, the U.S. DEA has recognized MDMA as the drug with the most rapidly expanding public use. Seizures of this drug have escalated dramatically in this time, and despite intensive efforts to disrupt trafficking in the drug, its use continues to increase.

A factor that appears to contribute to public use of MDMA is its undeserved reputation as a safe drug that has non-existent or very rare side effects (8). On the contrary, acute and chronic toxicity of MDMA is routinely observed. Typical effects of MDMA use include psychomotor stimulation, logorrhea, bruxism (9,10), and euphoria (11). Mild acute toxic effects include nausea, emesis, anxiety (12), and palpitations. Severe toxicity includes dysrhythmia, hyperthemia (13,14), rhabdomyolysis (15,16), hepatotoxicity (17-23), renal failure (24), hyponatremia (25,26), SIADH (27), intracranial hemorrhage (28,29), cerebral infarction (30), sudden cardiac death (31), serotonin syndrome (32,33), and seizures. Such toxicity, sometimes fatal, may result from a single "therapeutic" dose of the drug (34).

Of the toxic effects of MDMA, perhaps the most concerning is the well-documented neurodegenerative serotonergic toxicity, a unique effect associated with MDMA use

(35,36). The clinical results of chronic MDMA use include depression (38) and suicidal ideation (39), difficulty concentrating, impaired cognitive function (40,41), and memory loss (42). Investigations of such individuals reveal abnormal patterns of serotonergic function on positron emission brain imaging (43,44), diminished brain and CSF levels of serotonin and metabolites (45,47), and impaired cognition, particularly with memory (48-51) and language skills (52,53). An additional adverse effect associated with use of MDMA but not other amphetamines is SIADH and symptomatic hyponatremia (54-56).

Case Report

A 15 year-old girl was brought by ambulance to the pediatric ED of an urban hospital medical center with a complaint of altered mental status. Sixty hours prior to presentation she attended a party with high-school friends. At home that evening her parents observed her to be "fidgety and anxious" and that she had warm, flushed skin, and stated that she could not fall asleep. The following afternoon she finally fell asleep and she slept continuously for 18 hours. Upon waking she had slurred speech, slight disorientation, and restlessness that over the next 18 hours degenerated to confusion, stupor, and ultimately obtundation. She was then transported by ambulance to the ED.

The patient's past medical history was significant for intermittent anxiety of several months' duration. The parents denied any possibility of drug or alcohol use. The parents reported that the girl's fluid intake was not any greater than baseline. There were no known drug allergies and the patient took no medications or herbal preparations.

Upon arrival in the ED, the patient was obtunded. The patient's vital signs included: blood pressure 110/75 mm Hg; pulse 90 beats/minute; respiratory rate 14/minute; rectal temperature of 98.2°C and the patient had no orthostatic hypotension. There were no signs of head trauma. Examination the cranial nerves and peripheral neurologic examination was normal and non-focal excepting that the pupils were mydriatic, 9 mm and sluggishly reactive bilaterally. The patient had bruxism and increased masseter muscle tone, and her skin was flushed. The remainder of the physical examination was within normal limits. Her capillary refill and skin turgor were normal, and her mucus membranes were moist.

The fingerstick glucose measurement at the bedside was 45 mg/dL (2.5 mmol/L). In response to the serum glucose measurement, the patient was given orange juice to drink. Minutes after consumption of the orange juice, the patient's serum glucose was remeasured and determined to be 79 mg/dL (4.4 mmol/L), but there was no improvement in the mental status associated with this increase in serum glucose.

The patient was somnolent but occasionally would appear awake and alert. She could not readily answer questions verbally and her speech was mostly incomprehensible. In the times she was able to speak clearly, she typically muttered apparently confessional mutterings, such as "I did something bad." and "I have to tell you something I did".

A 12-lead electrocardiogram was normal. The patient's serum electrolyte concentrations were: sodium 123 mmol/L, potassium 3.3 mmol/L, chloride 87 mmol/L, bicarbonate 20 mmol/L, blood urea 9 mg/dL (3.2 mmol/L), creatinine 0.8 mg/dL (70.7 mmol/L). The urinary sodium concentration was 122mmol/L and urinary creatinine concentration was 25.7 mg/dL (2.27 mmol/L). The urinary fractional excretion of sodium was 3.04. In-hospital toxicology screening was negative for amphetamines, cannabinoids, cocaine, ethanol, opioids, phencyclidine, acetaminophen and salicylates. Analysis of cerebrospinal fluid revealed no leukocytes, no erythrocytes, glucose of 79 mg/dL (4.4 mmol/L), and total protein 24 mg/dL (2.4 mg/L). Gram stain and microscopy of the CSF revealed no organisms or abnormalities.

A presumptive diagnosis of MDMA-induced SIADH was made and the patient was managed by fluid restriction. Over 14 hours her serum sodium increased to 134 mEq/L (134 mmol/L) and her mental status normalized. Serum toxicology assay by enzyme multiplied immunoassay technique (EMIT) and subsequent confirmation by gas chromatography/mass spectrometry confirmed the presence of MDMA.

Discussion

MDMA-induced SIADH is an uncommon but well-reported phenomenon in adults. Few reports of pediatric cases exist. Early reports of symptomatic hyponatremia associated with MDMA uses were routinely attributed to "water intoxication" the putative cause being excess water intake (57). Controlled clinical trials have clearly demonstrated that all persons develop transient elevation in antidiuretic hormone levels after ingestion of MDMA (58). The presence of elevated ADH level has been clinically confirmed in MDMA-induced SIADH (59) and SIADH has been associated with other serotonergic agents (60). Because ADH release is mediated by serotonin, it is understandable that MDMA or other potent serotonergic agents may induce SIADH (61,62). Due to the clear evidence of elevated AHD levels associated with MDMA use, SIADH should be considered a cause of hyponatremia and hypoosmolality resulting from MDMA use.

The other putative cause of these metabolic derangements is free water intoxication resulting from excess water intake. The theory of free water intoxication appears to be based on the presumption that MDMA users drink excess free water when dancing or engaging in other activities while "high" on the drug and case reports of such patients that have ingested large quantities of water. Literature

of experimental or other evidence corroborating the theory of free water intoxication is lacking, and it is unclear if this phenomenon plays any role in MDMA associated hyponatremia and hypoosmolality.

A small fraction of patients exposed to MDMA develop SIADH with symptomatic hyponatremia and up to 20% of these cases are fatal. The preponderance of published accounts report MDMA associated hyponatremia and hypoosmolality in females, and it is the authors' experience that this phenomenon occurs almost exclusively in females. Increased sensitivity to ADH during times of depressed estrogen levels may be a particular risk factor for this phenomenon (63).

Diagnosis of MDMA-induced hyponatremia is based on hyponatremia and corroboration of MDMA use. Because many hospital laboratories may not have the capability of confirming the presence of MDMA in biologic samples, the corroboration of MDMA use may be based on history or a presumptive diagnosis may be made. The patient's history of developing symptoms of confusion the morning after attending a party is quite usual for MDMA-induced SIADH. Her physical examination findings of bruxism, mydriasis, and tachycardia were also typical of MDMA exposure. The clinical evidence of the patient's intravascular volume status suggested that she was euvolemic.

Although MDMA typically induces a hyperalertness and psychomotor stimulation, patients with MDMA-induced SIADH commonly present with depression of mental status ranging from confusion to obtundation. Cerebral edema may be demonstrated on non-contrast CT of the brain, but this image is not necessary to make the diagnosis and it is not known if this is consistently present in all patients with MDMA-induced SIADH.

Patients with MDMA-induced hyponatremia commonly present with altered mental status, which may be confusion, a mute state, coma, or even seizure (64). The importance of recognition of these and other presenting signs and symptoms of MDMA toxicity is paramount (65). Serum sodium levels of such patients are typically 115-125 mmol/L, though levels may be as low as 101 mmol/L (66). Additional laboratory evidence of SIADH includes elevated urinary excretion of sodium and increased fractional excretion of sodium. In euvolemic patients, this constellation of hyponatremia with inappropriate renal excretion of sodium is diagnostic of SIADH. However, it is possible that hypovolemic patients may experience hyponatremia with renal excretion of sodium, and in such a case the diagnosis of free water intoxication, although unlikely, is a possibility.

The focus of treatment of symptomatic hyponatremia resulting from MDMA-induced SIADH is supportive care and fluid restriction. Initially, an assessment of airway, breathing, serum glucose, and 12-lead ECG should be quickly performed to identify other factors causative of altered mental status. Patients who present with profound hypovolemia should be treated with intravenous normal saline. As SIADH is the likely cause of hyponatremia and hypoosmolality associated with MDMA use, great care should be taken to confirm the need for fluid resuscitation prior to administration. Infusion of fluid to a euvolemic patient with MDMA-induced SIADH and symptomatic hyponatremia is expected to exacerbate the condition, and the possibility of iatrogenic injury including fatality is quite real. The need for fluid restriction and dangers of fluid administration are strongly stressed. The lay press has even become informed about the dangers of fluid administration for MDMA-intoxicated patients; an increasing number of public health information has dropped recommendations that MDMA users drink additional water when using the drug (67).

Seizure is not typically associated with MDMA-induced SIADH, but the phenomenon has been well reported (68,69). In this setting, seizures from hyponatremia should be treated with hypertonic saline, with the goal of raising the serum sodium by 5 mmol/L. Although the concern of inducing central pontine myelinosis cautions clinicians against rapid correction of hyponatremia, in the setting of seizure, hypertonic saline may be administered relatively quickly, over a period of as little as 30 minutes.

Conclusions

MDMA is a widely and increasingly abused drug with both sympathomimetic and serotonergic properties and toxicities. Due to the increasing prevalence of MDMA, MDMA toxicity should be considered in the differential diagnosis of patients presenting with otherwise unexplained hyponatremia or SIADH, as well as patients with altered mental status in suggestive social circumstances.

SIADH and symptomatic hyponatremia is a unique feature of MDMA toxicity typically occurring in females the morning following drug use. The typical clinical presentation of such patients is altered mental status ranging from confusion to obtundation or coma. SIADH is a proven result of inappropriate ADH secretion in response to MDMA use. An additional putative but unproven cause of hyponatremia and hypoosmolality in such circumstances is excess free water intake. Management of otherwise uncomplicated MDMA-induced SIADH and symptomatic hyponatremia consists of fluid restriction and supportive care. Typically, fluid restriction results in correction of hyponatremia and resolution of symptoms in 12-24 hours (70).

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