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The "Ecstasy" Hangover: Hyponatremia Due to 3,4-Methylenedioxymethamphetamine

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ABSTRACT *3,4-Methylenedioxymethamphetamine (MDMA, or "ecstasy") has gained an undeserved reputation as a "safe" drug among its users. However, hyperthermia, rhabdomyolysis, hepatotoxicity, disseminated intravascular coagulation, long-term serotonergic neurotoxicity, and death are all associated with MDMA use. Hyponatremia is also reported, and its manifestations are frequently delayed several hours after the drug is ingested. The etiology of this hyponatremia is unclear; both the syndrome of inappropriate antidiuretic hormone release (SIADH) and free-water intoxication are advanced as explanations. We describe a 19-year-old female who presented to the emergency department with altered mental status 1 day after using MDMA. Her initial serum sodium was 121 mmol/L, and computerized tomography (CT) of her head demonstrated cerebral edema. She was treated with hypertonic saline and fluid restriction, and her serum sodium increased to 132 mmol/L over the next 24 hours. She regained consciousness completely within 48 hours of presentation and recovered uneventfully. MDMA toxicity, particularly the pathophysiology and treatment of MDMA-induced hyponatremia, are discussed.*

INTRODUCTION

3,4-Methylenedioxymethamphetamine (MDMA, or "ecstasy") is a frequently used recreational drug. In addition to the sympathomimetic effects expected from any amphetamine, MDMA also produces potent serotonergic effects. These serotonergic effects are the presumed mechanism by which MDMA engenders positive feelings and elevates the mood of users,[1] a quality that has been termed *entactogenic*.[2] This quality distinguishes MDMA from most other amphetamines.

Although MDMA has a reputation as a "safe" drug among its users, both acute and chronic toxicities are reported. In the acutely toxic patient, agitation and bruxism are common. Hyperthermia may be present,[3,4] and life-threatening temperature elevations as high as 43.3°C are reported after MDMA use.[4] Rhabdomyolysis may occur and may be either immediate[4] or delayed.[5–7] Acute liver toxicity in the absence of hyperthermia is also associated with MDMA use[8,9]; it may resolve spontaneously, or progress to fulminant hepatic failure necessitating liver transplantation.[3] Disseminated intravascular coagulation (DIC) is reported.[4] Deaths associated with acute MDMA toxicity have occurred.[3,10,11]

Chronic ingestion of MDMA leads to neurotoxicity, especially of serotonergic neurons. In monkeys, treatment with MDMA produces altered serotonin innervation patterns that persist for up to 7 years.[12] In humans, MDMA use is associated

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with depression,[13] impaired cognitive performance,[14] and abnormal patterns of serotonergic function on positron emission tomography (PET) scanning.[15] Cerebral spinal fluid studies in MDMA users demonstrate a reduction in the serotonin metabolite 5-HIAA (5-hydroxyindole acetic acid), further confirming serotonin toxicity.[16]

Another adverse effect associated with MDMA, but not with other amphetamines, is hyponatremia.[3,5,6,10,11,17–25] Although the pathophysiology of this hyponatremia is incompletely understood, it may be associated with significant morbidity[21,23] and mortality.[3,10,11]

We report a 19-year-old female who developed symptomatic hyponatremia after the ingestion of MDMA and discuss the clinical presentation, pathophysiology, and treatment of this disorder.

CASE REPORT

A 19-year-old female presented to the emergency department at 1 PM with a chief complaint of altered mental status. According to her boyfriend, she had been drinking alcohol and used one tablet of "ecstasy" between 10 PM and midnight the previous night. There was no report of other drug use, and no report of excessive water intake. At about 2 AM, she became drowsy and vomited several times. At 8 AM, she suffered a generalized seizure that lasted about 15 seconds. When she had not regained consciousness by noon, her boyfriend brought her to the emergency department.

On presentation, the patient was incoherent and unable to give a history. Vital signs were as follows: pulse, 85 beats/minute; blood pressure, 145/85 mm Hg; respiratory rate, 16/minute; temperature, 35.0°F. The HEENT (head, eyes, ears, nose, throat) examination showed no evidence of trauma. Examination of the neck showed no jugular venous distension. The cardiac examination was normal. The lungs were clear. The abdominal examination was unremarkable. The extremities were without peripheral edema. The neurologic examination was remarkable for profoundly decreased mental status, and the patient was responsive only to deep pain. Deep tendon reflexes and motor tone were normal.

The serum and urine chemistries are shown in the Table. The complete blood count was within normal limits. Noncontrast computerized tomography (CT) of the brain showed diffuse effacement of the sulci, consistent with cerebral edema.

TABLE. Serum and urine chemistries

	Serum	Urine
Sodium, mmol/L	121	111
Potassium, mmol/L	3.6	40
Chloride, mmol/L	90	108
Bicarbonate, mmol/L	18	—
BUN, mg/dL	4	—
Creatinine, mg/dL	0.5	—
Glucose, mg/dL	111	—
Osmolality, mOsm/L	242	485
Uric acid	3.7	—

BUN, serum urea nitrogen.

Urine toxicology testing was negative for barbiturates, benzodiazepines, cocaine, methadone, and opiates.

A working diagnosis of MDMA-induced hyponatremia was established. The patient was treated with intravenous hypertonic saline (3% NaCl) at a rate of 65 mL/h for 7 hours in conjunction with fluid restriction. Her mental status began to improve 24 hours after presentation, at which point her serum sodium was 132 mmol/L. After 48 hours, she was asymptomatic. She had no recollection of the early portions of her hospital stay, but was otherwise neurologically intact. Subsequent testing of the urine by gas chromatography/mass spectrophotometry confirmed the presence of MDMA.

DISCUSSION

As with all amphetamines, MDMA has a chemical structure that is similar to the endogenous catecholamine neurotransmitters epinephrine and norepinephrine. Like other amphetamines, MDMA causes central nervous system stimulation, tachycardia, hypertension, and dilated pupils[26] by stimulating the release of these endogenous catecholamines. MDMA is unique, however, in that it possesses more potent serotonergic properties, probably because of its structural similarity to serotonin. This "entactogenic" quality accounts for its current popularity.

During the early years of MDMA use, most of the reported complications were related to hyperthermia; as a result, many users considered water to be the "antidote" to MDMA toxicity. Proper hydration may in fact help prevent hyperthermia by preventing hypovolemia and may also prevent the renal complications of rhabdomyolysis. However, consumption of large amounts of free water might contribute to the development of hyponatremia.

The initial symptoms of hyponatremia, from any cause, may include nausea, vomiting, and muscle cramping. Later, as the serum sodium falls further, cerebral edema develops. In this stage, neurological findings predominate: headache, lethargy, confusion, obtundation, stupor, seizures, and coma are all recognized stages of the neurological dysfunction that accompanies hyponatremic cerebral edema.[27]

For diagnostic purposes, hyponatremic patients may be classified as euvolemic, hypovolemic, or hypervolemic. Euvolemic hyponatremia is usually caused by the syndrome of inappropriate antidiuretic hormone release (SIADH). Hypovolemic hyponatremia usually results from fluid and electrolyte loss, followed by replacement with hypotonic fluids such as water. Hypervolemic hyponatremia occurs with diseases such as cirrhosis and congestive heart failure, for which arterial underfilling initiates a complex neuroendocrine response that results in the retention of free water and hyponatremia.

In a normal individual, water metabolism is regulated by a number of factors, one of which is antidiuretic hormone (ADH). Normally, circulating ADH levels are low; hyperosmolar conditions and/or hypovolemia trigger ADH release. ADH causes water channels (aquaporins) to be expressed in the distal collecting duct of the nephron, leading to water reabsorption and returning osmolality and/or volume status toward normal. SIADH occurs when nonphysiologic processes such as pain, nausea, drugs, and primary central nervous system or pulmonary processes raise the serum SIADH levels in the absence of hyperosmolarity or hypovolemia.[28] This results in inappropriate water retention and subsequent hyponatremia.

There are several lines of evidence to support the theory that MDMA-induced hyponatremia is due to SIADH. MDMA is a serotonin agonist, and there is compel-

ling evidence that ADH release is mediated by serotonin.[29] First, other serotonergic agents, such as the selective serotonin reuptake inhibitors (SSRIs) are also associated with SIADH.[30,31] Also, when human volunteers are given MDMA, an increase in ADH levels is noted.[32] Finally, in one case report of MDMA-induced hyponatremia, an elevated ADH level was documented.[19]

Another theory is that MDMA-induced hyponatremia is caused by excessive water intake, which may occur for one of two reasons. First, uninformed users may believe that drinking copious amounts of water will "prevent" MDMA-induced hyperthermia, resulting in a psychogenic polydipsia that depresses serum sodium levels. Alternatively, some patients may develop hypovolemia after engaging in the frenetic dancing that frequently accompanies MDMA use, particularly at rave parties. In these patients, replacement of this fluid and electrolyte loss with free water may also lead to hyponatremia. In support of this theory, several published case reports of MDMA-induced hyponatremia mention that large amounts of water were consumed in conjunction with MDMA use.[7,10,11,22,23]

Unfortunately, distinguishing between these causative mechanisms can be very difficult. Some authors assert, erroneously, that a high urine sodium concentration coupled with a low serum sodium concentration is pathognomonic for SIADH in these cases.[6,17,18] In fact, this pattern can also occur with hypovolemic hyponatremia and is diagnostic for SIADH only in the presence of clinical euvolemia. As others have mentioned,[33] most case reports of MDMA-associated hyponatremia do not provide the clinical data—such as orthostatic vital signs, skin turgor, and mucous membrane status—necessary to establish euvolemia. This important data, which may not be rigorously sought in critically ill patients, was not recorded in this patient either. In the absence of such data, firm conclusions about the mechanism of hyponatremia cannot be drawn.

The diagnosis of MDMA-induced hyponatremia requires a history of MDMA ingestion and a serum sodium level less than 135 mmol/L. Patients with MDMA-induced hyponatremia commonly present with serum sodium levels of 115–125 mmol/L, although a sodium concentration as low as 101 mmol/L is reported.[22] In treating hyponatremic patients, however, care should be taken not to overinterpret a low serum sodium level. A comatose patient with a sodium level of 134 mmol/L, for instance, likely has another etiology for the depression in mental status.

Cerebral edema may be demonstrated on CT of the head, but this radiographic diagnosis is frequently difficult to establish. The findings associated with cerebral edema, such as blurring of gray-white junctions and effacement of the sulci, may be very subtle. Frequently, the diagnosis is only made in hindsight, when a follow-up head CT, in which the findings have resolved, is available for comparison.

Treatment of patients with MDMA-induced hyponatremia should begin with an assessment of the airway, breathing, and circulation. Rarely, patients will be so obtunded that they require intubation. Patients who present with profound hypovolemia should be cautiously volume resuscitated with a crystalloid such as 0.9% sodium chloride. As MDMA-induced hyponatremia may be due to SIADH, injudicious use of high-volume intravenous fluids in patients without hypovolemia should be avoided. Hypotonic fluids should never be used and may worsen outcome.[23]

Patients with seizures or an alteration in mental status due to hyponatremia should receive hypertonic saline (such as 3% NaCl),[34] with the goal of raising the serum sodium by 3–7 mmol/L; the time course of this correction depends on the nature of the patient's symptoms. In the presence of life-threatening symptoms,

such as seizures, this correction should occur at an hourly rate of 1–2 mmol/L. If symptoms are severe but not life threatening, such as lethargy, an hourly rate of 0.5–1.0 mmol/L is appropriate. Correction faster than this may result in central pontine myelinolysis (CPM), although this result is probably more common in patients with chronic hyponatremia that is corrected too quickly. Recently proposed suggestions for the administration of hypertonic saline[34] are provided in the Figure. The specific calculations for this case are also shown.

Once profound volume depletion is addressed and hypertonic saline (if needed) is administered, fluid restriction is the treatment of choice for MDMA-induced hyponatremia. This therapy is chosen because of the evidence suggesting that this disorder is caused by SIADH. Sodium levels generally return to normal in about 24 hours as the effects of the MDMA abate.

In the future, other treatment modalities may be effective. ADH antagonists have been developed,[35] and some authors have speculated that such agents may prove useful in the treatment of SIADH-induced hyponatremia.[36,37] These agents, however, are experimental and should not be considered part of the current treatment of MDMA-induced hyponatremia.

SUMMARY

3,4-Methylenedioxymethamphetamine (MDMA or ecstasy) is a widely abused drug with both sympathomimetic and serotonergic properties. Symptomatic hyponatremia is a unique feature of MDMA toxicity and is usually seen several hours after drug ingestion. It may result in altered mental status, cerebral edema, and death. Although there is strong evidence that this hyponatremia is due to SIADH, free-water intoxication may also play a role. Treatment generally involves securing the airway, breathing, and circulation; the administration of hypertonic saline to patients with seizure or lethargy; and fluid restriction. The serum sodium usually

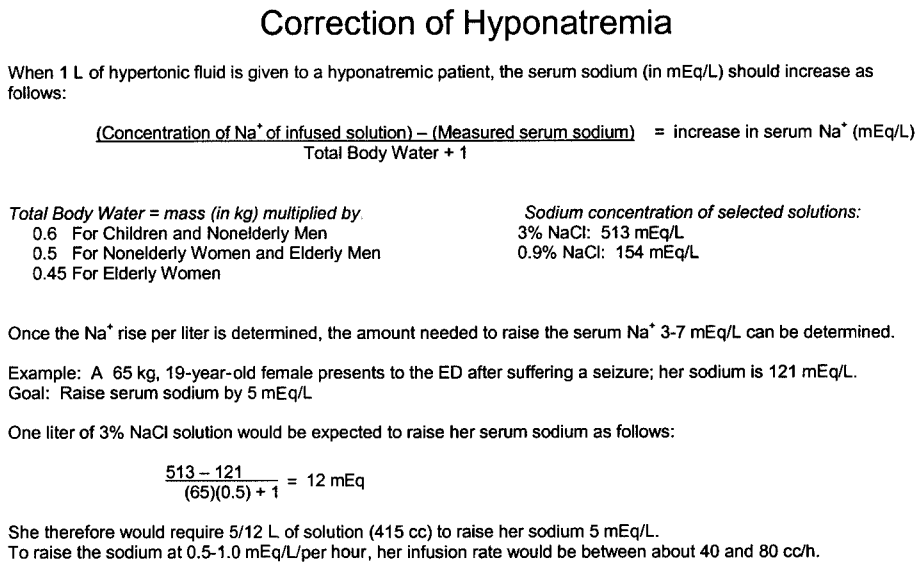

FIGURE. Correction of hyponatremia.

returns to normal over 24 hours. Clinicians should be aware that patients who present with altered mental status several hours after using MDMA may in fact be suffering from an "ecstasy hangover," symptomatic hyponatremia, rather than the direct effects of the drug itself.

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