

Hyponatremia Associated with 3,4-Methylenedioxymethylamphetamine ("Ecstasy") Abuse

MILOS N. BUDISAVLJEVIC, MD; LISA STEWART, MD; STEVEN A. SAHN, MD; DAVID W. PLOTH, MD

ABSTRACT: We present a case of acute, symptomatic hyponatremia in a young woman that developed after use of 3,4-methylenedioxymethylamphetamine (MDMA), more commonly known as "ecstasy." The patient was treated with 5% saline and had complete recovery. The pathogenesis of MDMA-associated hyponatremia involves excessive water intake and inappropriately elevated antidiuretic hormone (ADH) levels. It seems that young, premenopausal women are at particularly high risk for the development of severe, symptomatic hyponatremia after use of this drug. Review of the literature

revealed 4 fatal outcomes from MDMA-associated hyponatremia. All were women and all died from cerebellar tonsillar herniation. We suggest that acute hyponatremia that develops after MDMA use may be a life-threatening condition. Recent recommendation that MDMA users should drink large volumes of water may not be appropriate. **KEY INDEXING TERMS:** Hyponatremia; 3,4-Methylenedioxymethylamphetamine (MDMA); Ecstasy; Antidiuretic hormone (ADH); Cerebral edema. [*Am J Med Sci* 2003;326(2):89–93.]

Recreational use of 3,4-methylenedioxymethylamphetamine (MDMA), better known as "ecstasy," has gained increasing popularity among young people.^{1,2} It is commonly abused at "rave" parties, usually with intense dancing in a relatively hot environment. Serious short- and long-term complications, including death, have been reported with use of this agent.^{2–4} Although first described by Maxwell in 1993, the association of MDMA with hyponatremia is not widely appreciated.⁵ We present a case of acute, symptomatic hyponatremia in a young woman that developed after ingestion of this drug. Given the seriousness of hyponatremia that may be seen after MDMA use and the potentially devastating consequences of inappropriate treatment, we have included a review of published cases of hyponatremia associated with MDMA abuse.

Case Reports

A previously well, 18-year-old woman was admitted to the ICU because of altered mental status. At 11 PM the night before, she

took 1 tablet of "ecstasy" with several beers. On arriving home early in the morning, she experienced excessive thirst and consumed "a lot" of water. Over next several hours, she became anxious, remorseful, and mildly agitated with visual hallucinations. She vomited several times and by 10 AM had become lethargic and unresponsive. At the time of admission to the ICU 3 hours later, the patient did not respond to instructions and her arms were postured in a flexor position. She was intermittently agitated and exhibited pronounced bruxism. Temperature was 95.2°F (35.1°C), pulse was 68 beats/min and regular, respiratory rate was 14 breaths/min, blood pressure was 141/89 mm Hg, and weight was 65 kg. Pupils were dilated at 8 to 9 mm in diameter with sluggish response to light. Remaining findings on physical examination were unremarkable.

Laboratory data included serum sodium of 124 mmol/L, serum urea nitrogen of 8 mg/dL, creatinine of 0.4 mg/dL, glucose of 107 mg/dL, albumin of 4.0 g/dL, calcium of 7.9 mg/dL, phosphorus of 3.2 mg/dL, creatinine kinase of 580 IU/L (reference range, 30–135), aspartate aminotransferase of 55 IU/L (reference range, 14–36), and alanine aminotransferase of 28 IU/L (reference range, 9–52). Arterial blood gas analysis revealed pH 7.37, pCO₂ of 37 mm Hg, and HCO₃ of 21.5 mmol/L. Measured serum osmolality was 250 mOsm/kg. Other electrolytes, as well as total bilirubin, alkaline phosphatase, thyroid-stimulating hormone, and coagulation tests, were normal. Urinary sodium and osmolality were 185 mmol/L and 761 mOsm/kg, respectively. Urine drug screen was positive for amphetamine and negative for opiates, cocaine, or cannabinoids.

The clinical course and management of the patient is depicted in Figure 1. She was given 1 L of normal saline over 8 hours without improvement in mental status and deteriorating serum sodium to 120 mmol/L. Over the next several hours, her corrected serum sodium decreased to 118 mmol/L. (Measured sodium was reported to be 114 mmol/L; however, glucose in that sample was 349 mg/dL.) Nephrology consultation was requested, and she was given 480 mL of 5% saline i.v. over the ensuing 6 hours. During infusion of hypertonic saline, the patient excreted 1600 mL of

From the Nephrology Division, Division of Pulmonary and Critical Care Medicine, Medical University of South Carolina, Charleston, South Carolina.

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Correspondence: Milos N. Budisavljevic, M.D., Nephrology Division, Medical University of South Carolina, 171 Ashley Ave., Charleston, SC 29425 (E-mail: budisamn@musc.edu).

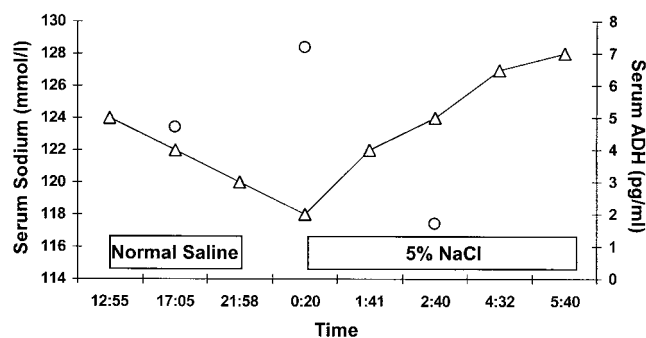


Figure 1. Serum sodium (Δ) and ADH ($\circ$) in patient with MDMA-induced hyponatremia. The ADH levels were inappropriately elevated, with values of 4.7, 7.2, and 1.7 pg/mL. Treatment with 5% saline resulted in improvement of hyponatremia.

urine with initial urine sodium concentration of 183 mmol/L. This approach resulted in improvement in serum sodium to 128 mmol/L. Over the next 24 hours, she excreted 4500 mL of urine with normalization of serum sodium. Serum toxicological testing performed more than 24 hours after ingestion failed to detect MDMA, and the level of methylenedioxymphetamine (MDMA metabolite) was 18 ng/mL. Although lagging behind the improvement in laboratory parameters, her mental status recovered slowly. She was discharged from the hospital without any obvious clinical or laboratory abnormality. Neuropsychological testing 1 month after MDMA ingestion showed minimal abnormalities; these disappeared by 3 months. Two years after the event, she is performing at a high academic level at a prestigious university.

Discussion

The ingestion of MDMA is associated with serious complications, including hyperthermia, disseminated intravascular coagulation, rhabdomyolysis, liver failure, cardiac arrhythmias, cerebral infarction, and psychiatric disturbances.²⁻⁴ Although in our patient creatinine kinase was mildly elevated, with peak value of 1381 IU/L, she had no signs of frank rhabdomyolysis. She developed acute symptomatic hyponatremia that resolved after treatment with hypertonic saline. Measured serum osmolality at 250 mOsm/kg with an osmolar gap of less than 10 mOsm/kg excluded the possibility of translocational or pseudohyponatremia. Furthermore, no signs of volume depletion were evident on physical examination, and her hyponatremia did not improve after treatment with normal saline. She had no thyroid, adrenal, cardiac, liver, or kidney disease. Urinary sodium concentration (185 mmol/L) that was greater than serum sodium concentration (120 mmol/L) indicated that the patient was in a state of negative free water clearance.^{6,7} Based on weight and serum sodium concentration, positive water balance was estimated to be 4.5 L (Appendix A). However, the reason for the decrease in serum sodium to 118 mmol/L after admission to the hospital was not immediately obvious. Hospital records revealed that no free water was administered and she was unable to drink. No significant hypokalemia was present;

unfortunately, however, urinary potassium excretion was not measured. She was given 1 L of normal saline; based on urine volume and urine sodium concentration, the change in serum sodium after this intervention should have been less than 2 mmol/L (Appendix B). A possible explanation for greater decrease in serum sodium could be unmeasured urinary potassium excretion. Furthermore, before admission to the hospital, she drank large quantities of water, and delayed absorption of some water could also have contributed to additional decrease in serum sodium. Assuming some contribution of the urinary potassium excretion, delayed absorption of approximately 500 mL of water could explain a calculated serum sodium that is very close to the measured value (Appendix B).

It seems that both excess water intake and the inappropriate presence of ADH are involved in the pathogenesis of MDMA-associated hyponatremia.⁸ Our patient, like many patients with MDMA-induced hyponatremia (Table 1), reported increased intake of electrolyte-free water. This is of particular concern because intake of large volumes of water is common in MDMA users to counteract hyperthermia. In addition to excessive water intake, the measurement of ADH in our case (Figure 1) supports the role of inappropriately increased levels of ADH in the pathogenesis of MDMA-induced hyponatremia. The ability of MDMA to directly stimulate ADH secretion has been demonstrated in normal volunteers.⁹ However, under this experimental condition, the rise in ADH was accompanied by small fall in plasma sodium concentration, and study subjects remained asymptomatic. This implies that additional water intake is necessary for the development of symptoms. It is possible that in patients who develop hyponatremia after MDMA use, additional stimuli of ADH release, such as nausea, vomiting, or anxiety, lead to higher ADH levels than those seen in healthy volunteers. Finally, it is also possible that in some cases of MDMA-associated hyponatremia, sodium loss and subsequent volume depletion caused by excessive sweating could contribute to the development of hyponatremia. Recently, the involvement of the gastrointestinal tract in the development of hyponatremia after MDMA use was proposed by Cherney et al.¹⁰ The authors speculate that initial secretion of sodium in the intestinal lumen is followed by absorption of electrolyte-free water. However, they provided no clinical, laboratory, or experimental evidence to substantiate their hypothesis. Furthermore, in the discussion of this hypothesis, they failed to consider contributions of urinary volume and sodium and potassium excretion. For these reasons, this hypothesis remains unconfirmed.

Although urinary sodium excretion was substantial in some cases (including ours), we do not believe that the pathogenesis of MDMA-associated hyponatremia includes the syndrome of cerebral salt wasting.¹¹ In this syndrome, hyponatremia usually de-

Table 1. Clinical Characteristics and Outcome of Patients with MDMA-Associated Hyponatremia

Age Sex	No. of Pills	Water Intake	Temperature (°C)	Sodium (mmol/L)		Osmolality (mOsm/kg)		Treatment	Outcome	Ref.
				Serum	Urine	Serum	Urine			
18 F	3	NA	“normal”	120	186	242	562	HS, Fr, WR	Recovery	14
27 F	2	“copious amounts”	NA	124	NA	267	NA	Fr	Death	15
26 M	1	“large volume”	NA	101	NA	248	NA	Fr, NS	Recovery	16
17 F	1	“several liters”	37.5	115	10	256	577	NS	Recovery	17
19 F	NA	NA	35.9	115	162	253	522	HS, Fr	Recovery	18
24 F	NA	NA	NA	113	153	240	639	WR	Recovery	19
20 F	1/2	NA	“normal”	119	145	263	491	WR, NS	Recovery	20
30 F	1	“large quantities”	34	117	1	NA	38	NA	NA	21
15 F	NA	“large quantities”	32.8	125	NA	NA	NA	NS, WR, Fr	Death	22
20 F	1	“large quantity”	“normal”	112	112	238	256	Mannitol	Recovery	8
15 F	NA	“large volumes”	“apyrexial”	119	6	256	655	WR	Recovery	23
16 F	NA	NA	NA	112	99	242	184	WR	Recovery	23
24 F	1	NA	38	120	68	258	365	HS	Recovery	24
23 F	1/2	NA	“no fever”	123	NA	NA	NA	Observation	Recovery	25
17 F	1 1/2	NA	37.5	130	NA	NA	NA	NA	Recovery	5
17 F	1	“5 liters”	“afebrile”	118	NA	247	970	Conservative	Recovery	5
23 F	1	“10 liters”	34.1	115	246	NA	NA	NS, glucose	Death	26
19 F	1	Unknown	35	121	111	242	485	HS	Recovery	27

F, female; M, male, NA, not available; HS, hypertonic saline; NS, normal saline; Fr, furosemide; WR, water restriction.

velops over 7 to 10 days, and ADH is elevated but only to levels appropriate for the level of volume depletion.¹² As discussed previously, volume depletion in our case was not present, and treatment with normal saline did not improve hyponatremia or decrease ADH levels (Figure 1). However, we did not evaluate fractional excretion of urate, which has been suggested to be of diagnostic value in this setting.¹³

Review of the literature identified 18 additional cases of hyponatremia associated with MDMA abuse (Table 1). Seventeen were young women 15 to 30 years old (median age, 19.5 years). The majority of them admitted taking only 1 pill (50–150 mg) of MDMA, usually with large quantities of fluid. All cases presented with severely altered mental status, and the interval from drug ingestion until onset of symptoms was short, between 4 and 24 hours. The serum sodium concentrations ranged from 101 to 130 mmol/L (median, 118 mmol/L). The median serum and urine osmolalities were 248 (range, 238–267 mOsm/kg) and 506 mOsm/kg (range, 38–970 mOsm/kg), respectively. A few cases had low urinary sodium and clinical signs of volume depletion that might have contributed to the development of hyponatremia.

MDMA abuse is associated with mortality ranging from 0.2 to 5.3 cases per 10,000 users in the United Kingdom.²⁸ According to the literature, the majority of deaths were caused by hyperthermia with disseminated intravascular coagulation.^{29–33} However, it has been suggested that the majority of patients who present with hyponatremia after MDMA use do not have elevated body temperature.³³ The review of

patients presented in Table 1, as well as a report by Milroy,³⁰ support such an argument. Only 1 of the reviewed patients had mildly elevated body temperature.²⁴ Three (17%) of the 18 reported patients with MDMA associated hyponatremia died (Table 1), and all were women.

Treatment of MDMA-associated hyponatremia deserves particular attention. In all reported cases, hyponatremia developed within 24 hours. As suggested by a number of different lines of evidence, acute, symptomatic hyponatremia, particularly in young women, is a serious condition with significant morbidity and mortality.^{34–36} There were no deaths in the reported cases of MDMA-associated hyponatremia who received treatment with hypertonic saline. However, 3 patients presented in Table 1 and an additional case of an 18-year-old woman reported by Hartung et al³⁷ who died were treated with furosemide,^{15,22,37} normal saline,^{22,37} water restriction,²² or other fluids.²⁶ All had cerebral edema and 3 had cerebellar tonsillar herniation at autopsy.

We strongly advocate treatment with hypertonic saline in symptomatic patients with MDMA-associated hyponatremia to reverse acute cerebral edema. Water restriction with or without loop diuretics may be employed in less severe cases but is inadequate treatment for symptomatic patients. Our case, as well as others reported in the literature, raises concern about the recommendation recently suggested for “providing plenty of water at rave parties.”¹

In summary, we describe a case of severe acute hyponatremia after ingestion of MDMA that was associated with elevated levels of ADH. The patient responded to treatment with hypertonic saline with

full functional recovery. We strongly suggest that serum sodium always be measured in symptomatic premenopausal women suspected of using ecstasy before management is undertaken.

Appendix A

Free Water Gain

Patient presented to the hospital with serum sodium of 124 mmol/L. Her weight was 65 kg.

$$\begin{aligned}\text{Total body water} &= 65 \text{ kg} \times 0.6 = 39 \text{ L} \\ (124 \text{ mmol/L} \div 140 \text{ mmol/L}) \times 39 \text{ L} &= 34.5 \text{ L} \\ 39 \text{ L} - 34.5 \text{ L} &= 4.5 \text{ L} \\ \text{Water excess} &= 4.5 \text{ L}\end{aligned}$$

Appendix B

Deterioration of Hyponatremia

Patient received 1 L of normal saline and excreted 1.5 L of urine with initial sodium concentration of 185 mmol/L. Expected decrease in serum sodium after this intervention should be less than 2 mmol/L:

$$\begin{aligned}124 \text{ mmol/L} \times 39 \text{ L} &= 4836 \text{ mmol/39 L} \\ 4836 \text{ mmol/39 L} + 154 \text{ mmol} + 1 \text{ L} &= 4990 \text{ mmol/40 L} \\ 4990 \text{ mmol/40 L} - 278 \text{ mmol (urinary sodium)} - & \\ 1.5 \text{ L (urine volume)} &= 4712 \text{ mmol/38.5 L} \\ 4712 \text{ mmol/38.5 L} &= 122.4 \text{ mmol/L}\end{aligned}$$

However, the patient's serum sodium dropped to 118 mmol/L. If we speculate that the patient had delayed absorption of 500 mL of water and excreted 52 mmol of potassium in addition to the recorded 278 mmol of sodium in 1.5 L of urine, calculated serum sodium reaches a value very near the measured one:

$$\begin{aligned}4836 \text{ mmol/39 L} + 154 \text{ mmol} + 1 \text{ L} + 0.5 \text{ L} & \\ (\text{delayed absorption}) &= 4990 \text{ mmol/40.5 L} \\ 4990 \text{ mmol/40.5 L} - 330 \text{ mmol (Urinary Na}^+\text{K)} - & \\ 1.5 \text{ L (urine volume)} &= 4660 \text{ mmol/39 L} \\ 4660 \text{ mmol/39 L} &= 119 \text{ mmol/L}\end{aligned}$$

Appendix C

Correction of Hyponatremia

Patient was given 480 mL of 5% saline and she excreted 1.6 L of urine with initial sodium concentration of 183 mmol/L. Serum sodium rose to 128 mmol/L.

$$\begin{aligned}118 \text{ mmol/L} \times 39 \text{ L} &= 4602 \text{ mmol/39 L} \\ 4602 \text{ mmol/39 L} + 411 \text{ mmol (sodium in 5\% saline)} &+ 0.480 \text{ L (volume of 5\% saline)} = 5013 \text{ mmol/39.48 L} \\ 5013 \text{ mmol/39.48 L} - 293 \text{ mmol (urinary Na)} - & \\ 1.6 \text{ L (urine volume)} &= 4720 \text{ mmol/37.88 L} \\ 4720 \text{ mmol/37.88 L} &= 125 \text{ mmol/L}\end{aligned}$$

The discrepancy between calculated and measured serum sodium (125 versus 128 mmol/L) is most likely explained by progressive decrease in urinary sodium concentration during 5% saline infusion with excretion

of less than 293 mmol of sodium. In fact, urinary sodium was 14 mmol/L 3 hours later.

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