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Case Challenge

A Rare Case of MDMA-Induced Hyponatremia

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A B S T R A C T

Hyponatremia is a common, potentially serious problem encountered in primary, acute, and critical care settings. Proper treatment requires an understanding of the multiple possible causes of hyponatremia. This case report presents an unusual cause of hyponatremia—3,4 methylenedioxymethamphetamine (MDMA; "Ecstasy" or "Molly") use. With encouraging research emerging on the use of psychedelic drugs to treat depression, anxiety, posttraumatic stress disorder, and addiction, nurse practitioners should increase their knowledge about the evolution of MDMA from a recreational drug to a potential medicine for the care of people with serious and persistent mental health concerns.

Arnold (not his real name), age 45, had a voracious appetite for substances, some legal and some not. Each day he drank 5 to 10 liters of diet coke and smoked >1 packs of cigarettes, and had a long history of heavy alcohol, cannabis, and psychedelic drug use. When our primary care practice met him, he reported almost daily use of 3,4 methylenedioxymethamphetamine (MDMA aka "Ecstasy" or "Molly") and occasional use of other psychedelics, including ketamine and psilocybin.

Arnold presented to primary care with a chief complaint of "hypertension" and an unusual story. He had been seen a few days earlier at a walk-in urgent care clinic after "not feeling right" at a group psychedelic ceremony the night before during which he had taken high-dose MDMA. Although he did not have a known history of hypertension, the ceremonial guide had prudently taken his blood pressure based on his symptoms. It was markedly elevated at 180/110 mm Hg. He was given alprazolam (dose unknown), and his blood pressure decreased to 124/85 mm Hg. Over the next few days, Arnold monitored his blood pressure at home and stated it fluctuated from normal to severely elevated. During this time, he also stated that he consistently felt "off," describing "moments when the words [he] heard in his head were not the ones coming out of [his] mouth." When he told a friend, they insisted that he immediately go to urgent care.

At the urgent care clinic, Arnold's blood pressure was 150/100 mg Hg with a resting heart rate in the 70s. He denied chest pain, palpitations, shortness of breath, headache, visual changes, or gastrointestinal/genitourinary symptoms, including oliguria. According to Arnold, no blood was drawn for laboratory assessment but the results of an examination of his heart and lungs and an electrocardiogram were "normal." Arnold was diagnosed with hypertension and anxiety, started on lisinopril, 10 mg once daily, and told to follow-up with his primary care provider within the week.

When he arrived at primary care 3 days later, Arnold was visibly anxious but not in acute distress. He stated he had used MDMA at least weekly, and often daily, for a number of years and had never had a similar experience. In fact, he felt that MDMA had had a measurably positive impact on his mental and physical health. For example, he had cut down on alcohol use significantly over the past year, from upwards of 30 drinks weekly to his current 1 to 2 drinks weekly. He had a history of heavy tobacco use (1 to 2 packs/day × 30 years), but stated that he had suddenly no longer wanted to smoke and had quit "cold turkey" 7 days before his visit (he continued to vape tobacco as part of his plan to achieve abstinence). And he also stated that participation in group psychedelic sessions had helped him develop more meaningful personal relationships with friends and family.

The only other recent major change in Arnold's life was a change in his caffeine intake. A few weeks earlier he had stopped drinking his usual 5 to 10 liters of Diet Coke (Coca-Cola Company) daily after friends voiced concerns about possible health implications of this intake. Since then, he had been substituting water in approximately the same amounts.

Medical History

Past medical history

Weight gain of 10 pounds in 6 months, moped accident in 20s without lasting impairments. No regular primary care or recent laboratory results known. States he had never been diagnosed with hypertension before or previously been told that his blood pressure was elevated. No serious or chronic illnesses as child.

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Past surgical history

none

Past psychiatric mental health history

Insomnia, anxiety—in talk therapy, intermittent use of alprazolam and other benzodiazepines given to him by a friend. Never received "official" psychiatric diagnosis or treatment.

Family History

Arnold was adopted as a newborn and does not know anything about his genetic history.

Social History

Social history

Single, no children, sexually active with women and men, no known history of sexually transmitted infections. Self-employed. Increased recent stressors due to some financial concerns and housing instability.

Substance use history

Regular use of synthetic cannabinoids (K2, spice), cannabis, MDMA, and various psychedelics, including psilocybin, ayahuasca, ketamine, and others (unknown). No opioid use. A ≥30 pack-year tobacco. Previous ≥30 alcoholic drinks per week; currently, ~1 to 2 drinks per week.

Diet

Omnivore; regular intermittent fasting in preparation for psychedelic use; mix of home cooked and restaurant meals.

Exercise

None.

Review of Symptoms

Denies headache, visual changes or aphasia
Denies sore throat, cough or congestion
Denies chest pain, palpitations, shortness of breath or lower extremity edema
Denies abdominal pain, diarrhea, constipation, nausea or vomiting
Denies recent joint pain, muscle pain or rash
Denies dysuria, polyuria or urinary hesitancy

Pertinent Physical Examination

Physical examination: Blood pressure, 145/86 mm Hg; heart rate, 85 beats/min; weight, 106.14 kg; height 185.42 cm 1 in (body mass index 30.89 kg/m^2).
General: Alert and oriented, appears his stated age.
Head, ears, eyes, nose, and throat: pupils equal round reactive to light and accommodation, oropharynx without erythema.
Neck: Supple without thyromegaly or lymphadenopathy.
Cardiac: Regular rate and rhythm, no murmur auscultated.
Respiratory: Normal air exchange without adventitious lung sounds.
Abdominal: Nontender/nondistended, no hepatosplenomegaly, no costovertebral angle tenderness.
Neurologic: Central nerves II-XI grossly intact, gait steady, negative Romberg.
Extremities: No edema noted.

Laboratory Data

Electrocardiogram: Normal sinus rhythm
Urine: chlorine 91 mEq/L (within normal limits); sodium, 19 mEq/L (28-720 mmol/L); osmolality, 125 mOsm/kg (within normal limits); creatinine, micro within normal limits;
Comprehensive metabolic panel: serum sodium, 127 mEq/L, otherwise within normal limits.

Case Challenge Questions

1. What is a "psychedelic session," and could use of psychedelics be related to this patient's symptoms?
2. What is the cause of this patient's hyponatremia and high blood pressure?
3. What workup is indicated for this patient's hyponatremia?
4. What treatment is indicated for this patient's hyponatremia?
5. What is the recommended follow-up?

Case Challenge Questions and Answers

1. What is a "psychedelic session" and could use of psychedelic drugs be related to this patient's symptoms?

For centuries, Indigenous cultures around the world have used psychedelic substances, such as peyote, ayahuasca, and psilocybin mushrooms, as part of community rituals, for physical and emotional healing, and as a way to connect to the spiritual world.[1] More recently, clinical trials have found promising results in the use of similar substances in the treatment of posttraumatic stress disorder, anxiety, depression, and addiction.[1] In response to these very encouraging early findings, the United States (US) Food and Drug Administration assigned breakthrough therapy designation to MDMA in 2017.[2] US Food and Drug Administration approval is widely expected for MDMA in 2023, with approval for psilocybin mushrooms not far behind. Ketamine has been used for treatment resistant depression since 2019.[3]

In parallel to clinical trial research, individuals and groups have been exploring many of the same psychedelic drugs in naturalistic settings, with the goal to improve health and well-being, explore spirituality, and/or alter consciousness. A 2013 study found that 17% of the adult US population had had at least 1 lifetime psychedelic experience.[4] The 2021 annual US survey of substance use found rates of psychedelic use soaring among young adults in the past decade.[5]

However, because most psychedelic drugs are still schedule I substances in the US (eg, classified as having high potential for abuse with no medical indications), there is still much we do not know about who is using psychedelics and why they are choosing to take them. As well, as in this case in which a patient took high doses of MDMA, little is known about the perceived and real risks and benefits of various psychedelics being used in naturalistic settings.[6]

Contrary to tales of the dangers of psychedelic drugs popular in the 1970s and 1980s, recent studies have suggested psychedelics have little to no addiction potential and few adverse effects.[7,8] In fact, research suggests that psychedelic drugs have a better safety

profile than many other psychoactive substances, including alcohol.[9,10] However, some case reports have documented rare adverse effects of varying severity. Rare adverse effects to MDMA, used by the patient in this case, may include allergy,[11] pyrexia,[12] hyperthermia and rhabdomyolysis,[13] and hyponatremia.[14] Thus, a 2022 National Academy of Medicine workshop report concluded that although psychedelics have significant potential for treating hard-to-manage mental health issues, more rigorous scientific and translational research is needed to fully understand safety and efficacy.[15]

2. What was this patient's diagnosis?

Arnold was diagnosed with (1) MDMA use disorder (*International Classification of Diseases* 10th Clinical Modification [ICD-10-CM] code F16.10); (2) elevated blood pressure, rule out hypertension (ICD-10-CM code R03.0); (3) elevated body mass index (ICD-10-CM code E66); and (4) acute hyponatremia secondary to MDMA use, water intoxication, antidiuretic hormone (ADH)-like (ICDM-10-CM code, E87)

3. What was the cause of this patient's hyponatremia?

Hyponatremia is a common electrolyte imbalance characterized by a serum sodium concentration of <135 mEq/L. Symptoms of hyponatremia range from none to malaise, nausea and mild confusion (as in this case) to lethargy, seizures, coma, and death.[16] In most cases of hyponatremia, there is a relative excess of water in relation to sodium, which produces extracellular hypotonicity. Less commonly, an excess of extracellular effective solutes, such as with hyperglycemia or pseudohyponatremia found in conditions such as hyperlipidemia and hyperproteinemia, leads to hyponatremia without hypotonicity.[14,17] Common causes of hyponatremia include adrenal crisis, hypothyroidism, alcoholism, hyperlipidemia, paraproteinemia, cirrhosis, cardiogenic pulmonary edema, and hypothyroidism.[14]

Hyponatremia is generally divided into 3 categories based on volume—hypovolemic, euvolemic, or hypervolemic, and then further categorized based on osmolality—hypotonic, isotonic, or hypertonic.[18] Hypotonic hyponatremia, as in this case, is caused by the excessive intake and retention of water. An excess of free water causes dilution of the extracellular fluid resulting in a serum osmolality of <275 mOsm/kg.

Two mechanisms are involved when there is an excess of free water. One mechanism involves the intake of large volumes of water >18 L/d or 750 mL/h and overwhelms the kidney's ability to excrete free water. The use of MDMA, water drinking contests, and psychogenic polydipsia are classic examples of this mechanism.

Another mechanism of free water excess is an intake of normal volumes of water that the kidneys cannot excrete for some reason. There are 3 mechanisms by which the excretion of free water is impaired. An excess of ADH activity is 1 mechanism that leads to free water excess.[14,19] An inability to suppress ADH is the common etiology in patients presenting with hyponatremia.[14,17] Conditions that cause high levels of ADH include syndrome of inappropriate antidiuretic hormone (SIADH), decreased renal perfusion, and cortisol deficiency, which stimulates the release of ADH. A low glomerular filtration rate is another mechanism that impairs free water excretion. Conditions with low glomerular filtration rate include acute and chronic renal failure. Lastly, low solute intake is another mechanism seen in malnutrition, where proteins and electrolytes, such as sodium, are less than is required for free water excretion.[14,19]

Hyponatremia can be a rare but serious complication of MDMA intoxication.[14] MDMA is a ring-substituted amphetamine that primarily acts as a releaser of presynaptic serotonin, oxytocin, and prolactin. MDMA has been noted for causing rare hyponatremia, as shown in this case (serum sodium, 127 mEq/L [normal, 135-145 mEq/L]); urine sodium, 19 mEq/L [normal, 20-220 mEq/L]). Rapid hyponatremia results in osmotic shifts of fluid into the cellular space, which can result in cerebral edema, altered mental status, and death. The decrease in sodium concentration with MDMA use has multiple causes. It is believed to be due to a combination of persistent secretion of ADH, which slows the rate of water excretion, and ingestion of an excessive amount of water to decrease the risk of Ecstasy intoxication, which produces such symptoms as hyperthermia and dehydration.[20,21]

Significant complications typically occur when serum sodium is <120 mEq/L. Because the laboratory tests occurred 3 days after MDMA use, it is possible that his symptoms of possible altered mental status, interpreted as anxiety in the psychedelic session, could have represented a more significant hyponatremia that was slowly resolving in the interim. Urine osmolality can help differentiate hyponatremia from water intake (urine osmolality <20 mmol/L) vs hyponatremia from an SIADH-like syndrome (urine osmolality >40 mmol/L).[22]

Nothing in the patient's history suggests that his hyponatremia is a result of polydipsia, and his urine osmolality is within normal limits, indicating that the hyponatremia was either preexistent or secondary to recent MDMA use—induced SIADH. However, his recent switch from Diet Coke (which contains 40 mg sodium per 8-oz serving) to water may have also contributed to the hyponatremia. Indeed, given his high intake, this patient's sodium intake was between 800 and 1,600 mg/d from Diet Coke.

As well, like other amphetamines, MDMA can have pressor effects that may have been a contributor, in conjunction with anxiety and acute caffeine withdrawal, to the hypertension observed on the day of the patient's MDMA session. The rapid response to alprazolam points to anxiety as being a significant contributor to the patient's high blood pressure.

3. What workup is indicated for this patient's hyponatremia?

Determining the etiology of hyponatremia requires a stepwise approach.[23] Patients with severe hyponatremia or overt neurologic symptoms should be evaluated in the emergency department because hyponatremia can be life threatening.

Step 1: History and physical. Inquire about the diet, fluid status, such as the presence of diarrhea, vomiting, use of diuretics, and the use of drugs, including illicit, nonprescribed, and prescribed. Evaluate vital signs for signs of dehydration, such as hypotension, orthostasis, tachycardia, and fever. An assessment of skin turgor, mucous membranes, edema, hepatomegaly, thyromegaly, ascites, lung lesions, and mental status is key to determining fluid status and identifying underlying conditions that would aid in determining the etiology of hyponatremia.

Step 2: Serum sodium.

Step 3: Serum osmolality, which helps determine if the hyponatremia is true, pseudo, or translocation.

Step 4: Urine osmolality to distinguish hyponatremia with normal urinary excretion or impaired free water excretion.

Step 5: Urine sodium: Determine whether sodium loss is renal or nonrenal.

Step 6: Urine-to-serum electrolyte ratio. This ratio is the sum of the urine sodium plus potassium concentrations divided by the

serum sodium concentration. A ratio of <0.5 (high urine electrolyte-free water) indicates a fluid restriction is required and sufficient; a ratio of >1 (urine is hypertonic compared with the serum) means water restriction alone will not correct the hyponatremia and other measures are necessary to do so.

Step 7: Fractional excretion of sodium (FENa), which accurately assesses volume status. In patients with normal renal function and hyponatremia, FENa will be <0.1%, in those with hypovolemic hyponatremia, FENa will be <0.1%, and in those with hypervolemic and normovolemic hyponatremia, FENa will be >0.1%.

Step 8: Serum uric acid and urea concentrations. Low serum uric acid and urea can determine the underlying cause of hyponatremia, and can result from conditions such as SIADH, hypopituitarism, thiazide-induced sodium loss, and hypervolemia. In hypovolemia, uric acid and urea may be normal or high.

Step 9: Acid-base and potassium balance. Obtaining an arterial blood gas and serum potassium concentration may help determine the etiology of sodium loss. For example, diuretic use or vomiting leads to metabolic alkalosis and hypokalemia; diarrhea or laxative abuse leads to metabolic acidosis and hypokalemia; primary adrenal insufficiency in patients without renal failure exhibit metabolic acidosis and hyperkalemia; in SIADH, there is normal acid-base potassium concentration, and in hypopituitarism because of higher plasma aldosterone levels, there is metabolic alkalosis and normal serum potassium.

Step 10: Saline infusion aids in the workup of hyponatremia. Hypovolemic hyponatremia will improve with administering normal saline, whereas SIADH will not and typically worsens.

4. What treatment is indicated for this patient's hyponatremia?

Rapid correction of sodium is recommended in patients presenting with acute hyponatremia due to the rare but real risk of hyponatremic encephalopathy and brain herniation. An otherwise healthy patient with mild hyponatremia, such as in this case, may be treated as an outpatient by limiting water intake and promoting renal water excretion.[16,24] Regular clinical and laboratory monitoring is essential due to documented risk for morbidity and mortality due to hyponatremia.

More serious cases require care in an emergency department or as an inpatient. The recommended treatment is 1 liter of 3% sodium chloride. Guidelines suggest administering a bolus of 100 mL of 3% sodium chloride over 3 minutes, repeating the same dose up to 3 times until acute symptoms abate. The goal is to increase serum sodium levels by 4 to 6 mmol/L to prevent brain herniation. Mild to moderate symptoms with a low risk of brain herniation may be treated less aggressively, with 3% sodium chloride infusion at 0.5 to 2 mL/kg/h.[23]

5. Case Follow-up and Conclusion

Arnold was able to rapidly correct his sodium through outpatient fluid restriction and electrolyte replacement. He followed-up daily until his serum sodium had returned to normal and all symptoms resolved. This would not have been possible had his sodium levels initially been <125 mEq/L, if his serum sodium levels continued to fall, if his neurologic symptoms worsened, or if there were concerns that he would not reliably follow-up as directed.

Arnold has continued to use psychedelics. He has a therapist with whom he discusses substance use, as well as other issues in his life. He has reduced his intake of water and restarted drinking Diet Coke, which contains sodium. He now abstains from alcohol completely and, over the past 6 months, has quit using all tobacco products. He has not had high blood pressure or hyponatremia since this episode.

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