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Brief Report

Transient proximal tubular renal injury following Ecstasy ingestion

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Abstract Multiple renal adverse effects have been anecdotally reported with the ingestion of 3,4-methylenedioxymethamphetamine (Ecstasy), a widely used recreational drug. These side effects include acute renal failure, necrotizing vasculitis, and hyponatremia, the mechanisms for which are unknown. We report a case of transient acute proximal tubular injury and hyponatremia associated with Ecstasy use. An 18-year-old woman presented with new onset seizures and polydipsia. Her initial laboratory evaluation revealed hyponatremia (Na 117 mEq/L), polyuria (urine output >400 mL/h for several hours), renal glycosuria (blood glucose 120 mg/dL, urine glucose >1,000 mg/dL), and solute diuresis (urine osmolality 552 mOsm/kg H2O). Urine electrolyte values reflected a low tubular reabsorption of phosphorus (TRP) of 68.1% (expected TRP >85% at serum P 2.3 mg/dL) with an appropriate transtubular potassium gradient of 3.0 (serum K 3.7 mEq/L). Her hyponatremia was slowly corrected. A repeat TRP after 48 h had normalized to 86.5%, and her glycosuria resolved. An extensive toxin screen was later

reported positive for Ecstasy. To our knowledge, this is the first example of an acute and transient proximal tubular injury with Ecstasy ingestion. This complication may become more apparent with increasing use of this drug.

Keywords Ecstasy - Hyponatremia - Proximal tubular injury

Introduction

An increasingly popular drug of abuse, 3,4-methylenedioxymethamphetamine (Ecstasy), has become prominent in today's club culture. Estimates of Ecstasy use in the college population range between 5 and 24% [1, 2], and its usage is showing rapid increases of up to 69% [1]. There have been numerous reports of multisystem toxicities following ingestion, including fatal events [3, 4]. Previously reported renal-related adverse effects include hyponatremia [3, 4, 5], necrotizing renal vasculopathy [6], acute interstitial nephritis [7], rhabdomyolysis [8], malignant hypertension [9], and disseminated intravascular coagulation with secondary acute renal failure [10, 11]. Fanconi syndrome, or proximal renal tubular dysfunction, has not been reported. We report a case of transient proximal tubular injury and hyponatremia in association with Ecstasy use.

Case report

An 18-year-old woman presented to the emergency department in the early morning with new-onset generalized tonic-clonic seizures. She had been to several nightclubs with friends the night prior to her admission. Her friends denied any alcohol or recreational drug use during the night. There was no history of trauma. They did note that upon arriving home, the patient had significant polydipsia. A few hours after coming home, the patient had generalized tonic-clonic seizures. She was taking no medications, and her past medical history was unremarkable. At presentation, she was postictal and somnolent; her vital signs were all within normal limits and her examination was unremarkable. In particular, there were no focal neurological deficits.

Her initial laboratory evaluation (Table 1) revealed hyponatremia (sodium 117 mEqL), hypoosmolality (245 mOsm/kg H2O), renal glycosuria (urine glucose >1,000 mg/dL, blood glucose 120 mg/dL), and solute diuresis (urine osmolality 552 mOsm/kg H2O and urine sodium 146 mEq/L). A cranial CT scan showed slightly small ventricles with no evidence of trauma. Over the first few hours of admission, she demonstrated significant polyuria (urine output >400 ml/h), and glycosuria was confirmed in multiple serial urinalyses over the next 24 h. Urine electrolyte values from a pretreatment sample reflected a low tubular reabsorption of phosphorus (TRP) of 68.1% when serum phosphorus was 2.3 mg/dL (expected TRP >85%). The transtubular potassium gradient (TTKG) of 3.0 was appropriate, with a serum potassium value of 3.7 mEq/L. The combination

of renal glycosuria and inappropriate phosphaturia demonstrated a proximal tubular injury, while the normal transtubular potassium gradient suggested normal distal tubular function. Serum phosphorus levels reached a nadir of 1.3 mg/dL prior to corrective measures. Her serum creatinine remained normal between 0.4 and 0.7 mg/dL, and she exhibited no other signs of impaired renal function or injury such as metabolic acidosis, hematuria, proteinuria, edema, or hypertension.

Her hyponatremia was slowly corrected over the next 24 h, and her mental status returned to baseline. Her polyuria also ceased several hours into her admission. During this time, the patient underwent further evaluation to elicit an etiology for her apparent acute proximal tubular injury. A screen for heavy metals, including lead, mercury and cadmium, was negative. Urine was negative for benzodiazepines, barbiturates, cocaine, and opiates. Also, the patient had normal thyroid-stimulating hormone and serum cortisol levels.

By the third day of hospitalization, the patient had returned to her normal state of health, and all of her electrolyte values had normalized. A repeat TRP at that time had normalized to 86.5% and her glycosuria had resolved. She was discharged home soon after. An extensive toxin screen had been sent on the day of admission and later returned positive for Ecstasy. The patient was seen in follow-up several weeks later. Her serum electrolytes and TRP remained normal (Table 1).

Discussion

Hyponatremia is well recognized in association with Ecstasy use, including some highly publicized lethal outcomes. The etiology of Ecstasy-induced hyponatremia is thus far unknown. Some evidence points towards increased vasopressin (ADH) secretion resulting in increased thirst and polydipsia. In healthy volunteers, Henry, et al. demonstrated a surge in ADH secretion 1–2 h after they ingested 40 mg of Ecstasy, with associated minimal decreases in plasma sodium levels. Further, Henry proposed that the link between Ecstasy and ADH may be via serotonin pathways, since Ecstasy stimulates serotonin secretion and ADH is in part regulated by serotonin [*12*].

Our patient similarly had hyponatremia with a history of polydipsia but with an associated transient proximal tubular injury. With cases of hyponatremia resulting solely from polydipsia, resolution of the hyponatremia occurs quite rapidly simply with fluid restriction. Also, in a syndrome of inappropriate secretion of antidiuretic hormone, one would expect diminished urine output. Our patient had a high urine output, but her hyponatremia was slow to improve. We propose that this may have been due to her solute diuresis resulting from her proximal tubular injury. While proximal tubular injury, chronic or acute, is not usually associated with hyponatremia, we believe in this situation, the proximal tubular injury may have acted as an exacerbating factor.

The mechanism by which Ecstasy could cause injury to proximal tubular cells is unclear but may relate to direct tubular cytotoxicity. Other types of Ecstasy-induced cellular injury have been reported, such as interstitial nephritis, rhabdomyolysis, and hepatitis. A direct cytotoxic effect may be attributed to Ecstasy itself, a

metabolite, or an additive. Animal studies have shown increased cellular oxidative stress with Ecstasy administration [*13*]. The proximal tubules have the highest energy consumption within the kidney and potentially may be at greatest risk for injury.

While this is only the first reported case of acute transient proximal tubular injury associated with Ecstasy use, it may be a coexisting complication in other cases of Ecstasy-associated hyponatremia.

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