

The Agony of Ecstasy: MDMA (3,4-Methylenedioxymethamphetamine) and the Kidney

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Ecstasy (MDMA, 3,4-methylenedioxymethamphetamine) is commonly used by college-aged individuals. Ecstasy leads to feelings of euphoria, emotional empathy, and increased energy. These effects come at a significant risk for complications. Ecstasy has been associated with acute kidney injury that is most commonly secondary to nontraumatic rhabdomyolysis but also has been reported in the setting of drug-induced liver failure and drug-induced vasculitis. More common, ecstasy has led to serious hyponatremia and hyponatremia-associated deaths. Hyponatremia in these cases is due to a “perfect storm” of ecstasy-induced effects on water balance. Ecstasy leads to secretion of arginine vasopressin as well as polydipsia as a result of its effects on the serotonergic nervous pathways. Compounding these effects are the ready availability of fluids and the recommendation to drink copiously at rave parties where ecstasy is used. The effects of ecstasy on the kidney as well as therapeutic measures for the treatment of ecstasy-induced hyponatremia are presented.

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Ecstasy (3,4-methylenedioxymethamphetamine [MDMA]) is a synthetic drug that has found widespread use in young adult populations (1,2). The compound (MDMA) was first synthesized in 1914 and originally developed as an appetite suppressant (3); however, the compound was never used for that purpose, and in the 1970s recreational drug use with MDMA was first noted (2). In 1985, the US Drug Enforcement Agency placed MDMA on schedule I of controlled substances, thereby restricting its use (4). This move was triggered from reports showing that the administration of a related analogue (a metabolite of MDMA, methylenedioxyamphetamine [MDA]) caused damage to serotonergic nerve terminals in rat brains and that the drug has a high abuse potential (4). MDMA (hereafter referred to as ecstasy) is most commonly used in night club environments or “rave” parties. A study of US college students conducted in 1988 found that 39% of students admitted to using ecstasy at least once in the past year (5). Ecstasy is taken for its mood-enhancing properties, which have been described as causing energy, empathy, and euphoria. These effects occur at a potentially significant cost. Medical complications as a result of ecstasy use are noted frequently in the literature (1,2). Unlike other drugs of abuse, the pattern of toxicity related to ecstasy is not attributable to overdose. Some individuals can use the drug without harm, whereas others, taking similar amounts, have experienced serious toxicity (1,6). The risk for death from ecstasy in first-time users has been estimated to be between one in 2000 and one in 50,000 (7). This review summarizes the available literature on the renal effects of ecstasy.

Pharmacology

Ecstasy (MDMA) is an amphetamine derivative. Numerous ecstasy-related compounds have been described: 3,4-Methylenedioxyethamphetamine (MDEA, or “eve”) and 3,4-methylenedioxyamphetamine (MDA, or “ice”) (8,9). Ecstasy causes release of neuroactive compounds such as serotonin (5-hydroxytryptamine), dopamine, and norepinephrine into the central nervous system (CNS) (1,8). Furthermore, neuronal uptake of these neurotransmitters, most notably with serotonin, is inhibited by ecstasy. These actions result from the interaction of MDMA with the membrane transporters that are involved in neurotransmitter reuptake and vesicular storage systems (8). The net result of these CNS effects is to increase acutely the levels of these neurotransmitters at the synapse. These effects on neurotransmitter levels lead to many of the effects that are induced by ecstasy use, including mood changes and thermoregulation and autonomic nervous system dysfunction. Ecstasy has also been documented as causing an increase in serum levels of prolactin, arginine vasopressin (AVP or ADH), cortisol, and adrenocorticotropic hormone (8,10) (summarized in Figure 1).

MDMA is metabolized by two main pathways (Figure 2) (8). The first pathway involves N-dealkylation, deamination, and oxidation, which is followed by conjugation with glycine. The second pathway involves O-demethylation followed by catechol-O-methyltransferase (COMT) catalyzed methylation. This second pathway involves the cytochrome P450 system isoenzyme CYP2D6 and shows genetic variance throughout the population (8). Those who show slow metabolism through this enzymatic pathway are at higher risk for acute toxicity because levels of MDMA remain elevated for a prolonged period of time (8). Even in patients who are not genetically poor metabolizers, the metabolites of MDMA can form inhibitor complexes with the CYP2D6 enzyme (8). Over

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Ecstasy and its sister compounds

MDMA, 3,4-methylenedioxyamphetamine, (“ecstasy”)	<p>Increased CNS levels of: Serotonin Norepinephrine Dopamine</p> <p>Increased blood levels of: Cortisol Arginine vasopressin Dehydroepiandrosterone Prolactin Adrenocorticotropin</p> <p>Activity at the following receptors: H1 histamine receptor 5-HT2 receptor M1 muscarinic receptor α-2 adrenergic receptor</p> <p>Other effects MAO inhibitor Tryptophan hydroxylase inhibitor Decrease in CD4-T lymphocytes Inhibit T cell responsiveness</p>
MDEA, 3,4-methylenedioxyamphetamine, (“eve”)	
MDA, 3,4-methylenedioxyamphetamine (“ice”)	

Figure 1. 3,4-Methylenedioxyamphetamine (MDMA) and related compounds on their effects on neurotransmitters and hormones. CNS, central nervous system; MAO, monoamine oxidase.

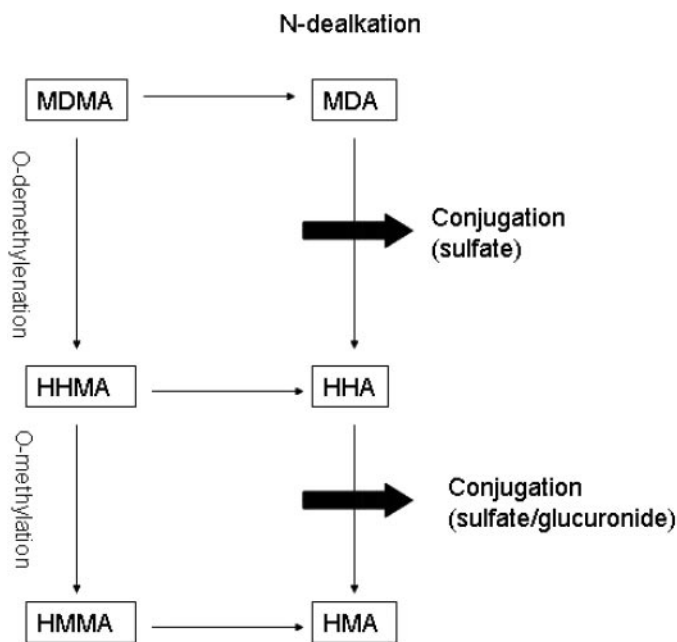


Figure 2. Metabolic pathways for MDMA. HHA, 3,4-dihydroxyamphetamine; HHMA, 3,4-dihydroxymethamphetamine; HMA, 4-hydroxy-3-methoxyamphetamine; HMMA, 4-hydroxy-3-methoxymethamphetamine; MDA, methylenedioxyamphetamine.

multiple doses (even as few as two doses), these inhibitor complexes lead to important changes in the metabolism of the drug and the potential for increased toxicity with repeated dosing (1,8). It also should be noted that many medications, including antiretroviral drugs such as protease inhibitors (e.g., ritonavir) and antifungal medications, are inhibitors of CYP2D6 and thus increase the potential for ecstasy toxicity (1,11,12). Given these factors, prolonged effects can be seen with even small doses of MDMA. COMT

activity is also subject to genetic variation (8). Included in the metabolites in the COMT pathway of degradation is a major metabolite, 4-hydroxy-3-methoxymethamphetamine (HMMA). HMMA has been documented as a more potent inducer of ADH secretion (13–17). As discussed next, the effects of this metabolite on the pituitary could explain the variable incidence of hyponatremia seen in ecstasy users.

Clinical Syndromes Associated with Ecstasy

A number of both minor and serious clinical symptoms and syndromes are associated with ecstasy ingestion (Table 1). Most of these symptoms are related to disturbances in the CNS and autonomic nervous system. The most frequent effects after ecstasy administration are euphoria, a sense of well-being, happiness, increased energy, extroversion, feeling close to others, increased empathy, increased sociability, mild perceptual disturbances, and somatic symptoms related

Table 1. Clinical syndromes associated with MDMA^a

CNS	acute: hyperactivity, lack of appetite, jaw clenching, dry mouth, increased thirst, restlessness, palpitations, impaired balance, difficulty in concentration, dizziness, drowsiness, nystagmus, hot flashes, muscular tension, weakness, insomnia, confusion, anxiety, tremor serious acute: panic attacks, delirium, psychosis, depression chronic: serotonin depletion, neurotoxicity, chronic psychosis, cognitive defects
Cardiovascular	hypertension tachycardia tachyarrhythmias sudden death cardiac ischemia cardiomyopathy
Gastrointestinal	acute hepatotoxicity fulminant hepatic failure
Renal	AKI hyponatremia
Musculoskeletal	rhabdomyolysis (may have associated disseminated intravascular coagulation)
Endocrine	hypoglycemia lower testosterone levels
Pulmonary	pneumothorax pneumomediastinum

^aAKI, acute kidney injury; CNS, central nervous system; MDMA, 3,4-methylenedioxyamphetamine.

to its cardiovascular and autonomic effects (BP and heart rate increase, mydriasis) (18). Acute side effects that are most often reported include lack of appetite, jaw clenching, dry mouth, increased thirst, restlessness, palpitations, impaired balance, difficulty in concentration, dizziness, drowsiness, nystagmus, hot flashes, muscular tension, weakness, insomnia, confusion, anxiety, and tremor. There are also more severe syndromes, including those associated with sudden death as a result of cardiac causes, severe hyperpyrexia, severe liver toxicity, and cerebral edema as a result of hyponatremia (1,19–24). As discussed in other review articles, there are also concerns regarding long-term neuronal and psychologic toxicity in long-term ecstasy users (19).

Acute Kidney Injury Associated with Ecstasy

Acute kidney injury (AKI) has been associated with ecstasy use (25) (Table 2). Because most of these data are accrued from case reports, the absolute incidence of this complication cannot be determined. The first case report of AKI associated with ecstasy use was reported in 1992 (25). This patient developed AKI after ingesting three doses of ecstasy at a rave party. In this case, the AKI was likely attributable to rhabdomyolysis in the setting of seizures as well as a direct toxic effect of the drug on myocytes. Furthermore, this patient developed disseminated intravascular coagulation, which was likely contributory in the development of AKI (25). This case represents the most common scenario that is associated with the development of AKI: Nontraumatic rhabdomyolysis (1,2). Rhabdomyolysis is likely secondary to ecstasy-induced seizures or repetitive muscular activity or perhaps due to a direct toxic effect of the drug on skeletal myocytes (26). In the majority of these cases, patients have been exerting themselves to excessive levels with inadequate hydration compounded by impaired thermoregulation and hyperpyrexia (6,27–29). The hyperpyrexia is likely due to activation of 5-hydroxytryptamine and dopamine receptor systems, which are effectors of thermoregulation and activate mechanisms that both conserve and generate heat (30,31). Another mechanism may be related to the effects of MDMA to uncouple skeletal muscle mitochondria *in vivo*, generating increased thermogenesis (26,32). These effects on thermogenesis are greatly compounded by

the ambient temperature, which in crowded rave parties is usually elevated. Elevations of creatinine phosphokinase in these cases can be pronounced with levels $\geq 100,000$ U/L (1). Volume depletion and hypotension further compound the nephrotoxic insult of myoglobinuria. In some cases, disseminated intravascular coagulation occurs and is likely contributory in the development of AKI (25,33).

Treatment of rhabdomyolysis associated with ecstasy follows standard protocols (34). In addition to treatment with aggressive hydration to maintain adequate urine output, the patient's hyperpyrexia must be addressed. Aggressive cooling measures should be undertaken to lower the patient's core temperature to levels that will lessen further muscle and end-organ injury. Dantrolene has been used with some success for ecstasy-associated hyperpyrexia, as in malignant hyperthermia (35–38).

Isolated proximal tubule dysfunction after ecstasy use has also been described in a single case report of an 18-yr-old who developed transient glycosuria, phosphaturia, and a solute diuresis (39). The mechanism of this nephrotoxic effect is unknown. MDMA and its metabolites are primarily excreted *via* the kidney, and MDMA in a rat model has been shown to lead to a dosage-dependent production of proximal tubular injury (40). In that model, there was an absence of an inflammatory infiltrate. A proposed mechanism is that MDMA metabolites [α -methyldopamine and 5-(glutathione-S-yl)- α -methyldopamine] undergo oxidation to o-quinone, which is toxic to proximal tubular cells (40,41). This oxidative stress may independently lead to or potentiate other causes (rhabdomyolysis) that lead to AKI. Unfortunately, no case reports of AKI secondary to ecstasy have had renal biopsies performed to allow for further elucidation of a possible nephrotoxic effect of the drug.

Fulminant hepatic failure secondary to ecstasy use has been reported, and these patients are at risk for the development of AKI secondary to the hepatorenal syndrome (42,43). A study by Andreu *et al.* (24) suggested that up to 31% of all drug toxicity-related acute hepatic failure is due to MDMA (with only anti-tuberculosis drug toxicity occurring more frequently). Patients with severe acute hepatic failure secondary to ecstasy use often survive with supportive care and have successfully undergone liver transplantation (42,43).

Other causes of AKI include a case of necrotizing vasculitis in a 30-yr-old man with negative serologies (44). In that case, the patient had used ecstasy 10 d before presentation and developed ESRD despite an empirical course of immunosuppressant medications. Further evidence that links the occurrence of a necrotizing vasculitis with ecstasy use includes a report of transplant graft loss of both kidneys obtained from a donor with a history of recent ecstasy use (45). On pathologic evaluation, graft loss was found to be secondary to necrotizing vasculitis with no other cause found despite an extensive work-up. Attributing causation to ecstasy in these cases is difficult because many users of this drug may be abusers of other substances. Furthermore, there are case reports of other drugs of abuse leading to vasculitis (46).

Table 2. Causes of AKI with ecstasy

Nontraumatic rhabdomyolysis secondary to hyperpyrexia secondary to extreme exertion secondary to direct toxicity (unknown)
Necrotizing vasculitis (rare case reports)
Obstructive uropathy secondary to bladder neck obstruction (one case report)
Malignant hypertension
Proximal tubule dysfunction (one case report)
Volume depletion (from sweating, hyperpyrexia)

Ecstasy use has been associated with bladder neck dysfunction, causing AKI secondary to obstruction (47). AKI may also be seen as a secondary event in cases in which ecstasy use induced accelerated or malignant hypertension (48).

Hyponatremia and Ecstasy

One of the most serious medical complications of ecstasy abuse is related to symptomatic hyponatremia (usually associated with a serum sodium <130 mEq/L) (48–68). This complication was first described by Maxwell *et al.* (52) in 1993, and since then, more than 25 separate case reports have been published (48–68) (Table 3). In those cases, the serum sodium on presentation ranged from 101 to 130 mEq/L, and the vast majority of cases occurred in female individuals who were between the ages of 15 and 30 yr and ingested a single dose of

ecstasy. The cause of hyponatremia seen with ecstasy is dilutional in nature and likely due to several interacting effects (Figure 3).

Excessive water intake has been directly associated with ecstasy use. This is due, in part, to an inadvertently harmful response to the hyperpyrexia seen with ecstasy use: The institution of “chill out” areas at clubs and raves (66). These areas feature free or reduced-priced water or low-solute-content drinks (*e.g.*, sports beverages), which can be obtained with the goal of hydrating to prevent hyperpyrexia and volume depletion. The ready availability of fluids is compounded by the effects of amphetamines to induce dry mouth and the sensation of thirst. Whether ecstasy leads to a primary drive to drink secondary to its CNS effects is not known but has been hypothesized (66,67). In one dramatic case, an 18-yr-old woman pre-

Table 3. Summary of reported cases of ecstasy-associated hyponatremia^a

Age	Gender	Sodium		Osmolality		Symptoms	Intervention	Outcome	Reference
		Serum	Urine	Serum	Urine				
18	F	120	186	242	568	A, C	H, F, R	Recovered	(78)
27	F	124	NA	267	NA	A, C	F	Death	(60)
26	M	101	NA	248	NA	C, S, P	F, N	Recovered	(51)
17	F	115	10	256	577	A, C, S	N	Recovered	(61)
19	F	115	162	253	522	S, P	H, F	Recovered	(49)
24	F	113	153	240	639	A, C, S	R	Recovered	(56)
20	F	119	145	263	491	A, C, S	R, N	Recovered	(79)
30	F	117	1	NA	38	A, C, S	NA	NA	(62)
15	F	125	NA	NA	NA	A, RA, P, C	N, R, F	Death	(54)
20	F	112	112	238	256	A, C	Mannitol	Recovered	(57)
15	F	119	6	256	655	A, C	R	Recovered	(53)
16	F	112	99	242	184	A, C	R	Recovered	(53)
24	F	120	68	258	365	A	H	Recovered	(50)
23	F	123	NA	NA	NA	A	Observation	Recovered	(64)
17	F	130	NA	NA	NA	A	NA	Recovered	(52)
17	F	118	NA	247	970	A, E	Conservative	Recovered	(52)
23	F	115	246	NA	NA	C	N, glucose	Death	(80)
19	F	121	111	242	485	A, C	H	Recovered	(81)
16	F	NA	NA	NA	NA	A	NA	Death	(82)
18	F	NA	NA	NA	NA	CA, HT	NA	Death	(82)
18	M	NA	NA	NA	NA	A, HT	NA	Death	(82)
14	F	NA	NA	NA	NA	CA	NA	Death	(82)
16	F	NA	NA	NA	NA	A, CA	NA	Death	(82)
29	F	NA	NA	NA	NA	CA	NA	Death	(82)
16	F	123	NA	NA	NA	S, LBP, C, P	NA	Death	(82)
20	F	119	NA	NA	NA	LBP, LT, RD	NA	Death	(82)
20	F	124	NA	NA	NA	A, C	NA	Death	(82)
19	M	122	NA	NA	NA	A, C	NA	Death	(82)
19	F	NA	NA	NA	NA	CA	NA	Death	(83)
19	M	NA	NA	NA	NA	HT, LBP, AKI	“Saline”	Death	(84)
20	F	117	NA	245	NA	CA	N, H, F	Death	(65)
18	W	130	101	264	335	HA	R	Recovered	(66)

^aA, altered mental status; C, cerebral edema; CA, cardiac arrest; E, electrocardiogram abnormalities; F, furosemide; H, hypertonic saline; HA, headache; HT, hyperthermia; LBP, hypotension; LT, hypothermia; N, normal saline; NA, not available; P, pulmonary edema on chest x-ray; R, water restriction; RA, respiratory arrest; RD, respiratory depression; S, seizure.

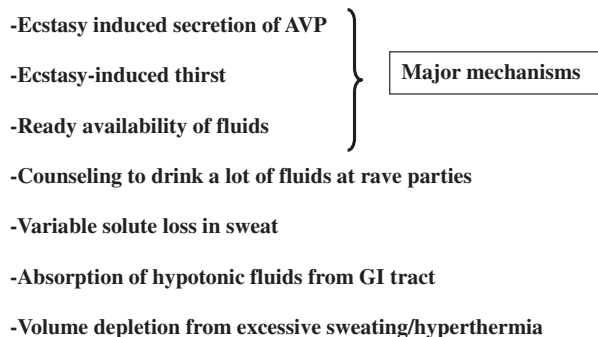
Factors involved in the pathogenesis of ecstasy-associated hyponatremia

Figure 3. Factors that are involved in the pathogenesis of ecstasy-associated hyponatremia. AVP, arginine vasopressin; GI, gastrointestinal.

sented to the emergency department soon after ingesting five tablets of ecstasy (66). She complained of a severe headache and thirst. Her initial serum sodium level was 136 mEq/L. Soon afterward, she consumed 1700 ml of water in an effort to satisfy her thirst and developed a worsening headache with repeat laboratory work showing serum sodium of 130 mEq/L. Of note, her urine osmolality was 335 mOsm/kg, her urine sodium was 101 mEq/L, and her plasma AVP levels were extremely high (33.7 pmol/L [normal <5.6 pmol/L]). The ready availability of hypotonic fluids, severe thirst, and counseling to drink copiously are likely not enough to lead to hyponatremia, because the ability of the kidney to excrete free water rapidly is usually greater than intake in most circumstances. Impairment of renal free water excretion must also occur as signified by the elevated urine osmolality and AVP levels in this and other cases (Table 3).

Ecstasy has been shown both in case reports and in controlled experimental settings to induce the secretion of AVP (13,49,50,57,59,64,65,67,69–72). Even in cases without documentation of AVP levels, urine osmolalities were inappropriately elevated in the setting of serum hypo-osmolality (range in case reports from 184 to 970 mOsm/kg), signifying the presence of AVP (reviewed in reference [64]). Henry *et al.* (13) administered relatively small doses of MDMA (40 mg, as compared with a common “street dose” of 100 mg) to eight normal volunteers and showed a statistically significant increase in AVP levels (from a baseline range of 1.14 to 1.88 pmol/L to 2.46 to 9.16 pmol/L) within 1 to 2 h after administration. This was accompanied by a slight fall in serum sodium and a rise in urine osmolality in these individuals that directly correlated with the rise in AVP. Several other controlled studies also documented a significant rise in AVP within 1 to 2 h after ecstasy administration (13,69–72). It is interesting that there is a significant negative correlation between MDMA levels and plasma AVP concentrations, suggesting that the major effect on AVP secretion may be mediated by a metabolite of MDMA (69,70,71). Those studies demonstrated that the parent compound MDMA could lead to AVP release but that HMMA (a major metabolite of MDMA) was significantly more potent in this ability (69,70,71). Because the demethylation of MDMA to HMMA is

mediated by the cytochrome P450 2D6 system, the metabolizer status (extensive or poor) of an individual could determine individual susceptibility in AVP secretion with MDMA ingestion (with the more extensive metabolizers producing a larger rise in AVP levels). Given the predominance of women in the case reports of ecstasy-induced hyponatremia, it seems logical to ask whether there are gender-specific effects on P450 2D6 activity; however, a review of the literature could find no such descriptions of such a gender effect. Finally, it should be noted that the rise in AVP in response to MDMA in these controlled settings was likely not due to any accompanying volume depletion (which may be a factor in individuals who take ecstasy in rave environments and typically develop hyperthermia and profuse sweating).

The mechanism of ecstasy-induced AVP release likely involves the serotonin system. Animal studies have shown that MDMA and its metabolites lead to the secretion of serotonin in the CNS (1). Furthermore, serotonin leads to the physiologic release of AVP from the neurohypophysis, thus linking MDMA and its metabolites to this effect (67). Given that MDMA has effects on monoaminergic neuronal transmission, it is possible that dopamine or norepinephrine may also have effects on AVP release (73,74); however, data on the effects of dopamine on AVP release have been contradictory, and the response to norepinephrine is unclear (73). AVP secretion may also be directly stimulated by stress, physical activity, and the use of nicotine, all of which are common exposures in the rave environment (75).

Although the combination of increased fluid intake associated with a concomitant rise in AVP levels will lead to hyponatremia, other mechanisms may be involved. First is the possibility that increased sweat sodium losses as a result of increased exertion, compounded by ecstasy-induced hyperthermia, can lead to significant sodium losses. This is likely marginal in its effect. The majority of case reports of ecstasy-induced hyponatremia do not have significant hyperthermia associated with them. Furthermore, assuming an hourly sweat loss of ≥ 2 L, with an estimated sweat sodium concentration of 45 mEq/L, massive amounts of sweat would need to be lost to create a large sodium deficit. Sweat is also hypotonic; therefore, sweat losses alone would tend to raise the serum sodium if this were the only factor in water balance. However, these losses are usually accompanied by ingestion of fluid with a lower tonicity of sweat (59). If sweat losses were extreme, then they could lead to volume depletion and potentiate the effect of MDMA on AVP secretion; however, it is the increased water ingestion along with urinary free water retention that is the main driving force leading to hyponatremia.

Another source of positive water balance has been suggested by Cherney *et al.* (59). In a quantitative analysis of hyponatremia as a result of ecstasy, they pointed out that if gastrointestinal tract motility were slowed by ecstasy, resulting in a large pool of electrolyte-poor water in the intestinal lumen, then this water could be rapidly absorbed at the end of activity and lead to a large, acute free water bolus, which, in the setting of high AVP levels, would drive down the serum sodium.

Another putative mechanism for ecstasy-associated hypona-

tremia is a direct effect of the drug on the expression of aquaporin 2 channels in the inner medullary collecting duct, as has been demonstrated with fluoxetine (76). This would lead to a direct increase in water reabsorption independent of ADH levels.

Acutely, the fall in serum sodium leads to the osmotic shift of water intracellularly with the resulting risk for cerebral edema and its associated complications such as mental status changes, seizures, coma, pulmonary edema (Ayus-Arieff syndrome [77]), and brain stem herniation resulting in death. In ecstasy users, female gender has been highly associated with increased odds for developing significant hyponatremic symptoms (Table 1). A review of published case reports and series revealed that >85% of symptomatic hyponatremic patients were female. This also was documented in a case review of emergency department admissions in California during a span of 5 yr. This study documented that women had a significantly higher incidence of symptomatic hyponatremia, coma, and death when seeking medical attention with complications of ecstasy use (49). This gender difference does not reflect a bias toward more female users of ecstasy, because other medical complications associated with ecstasy use are more frequent in male individuals. It is interesting that this gender difference has been seen in other causes of hyponatremia such as that occurring postoperatively (85,86). The gender susceptibility to the effects of hyponatremia may be secondary to the effects of estrogen to inhibit cerebral membrane Na-K-ATPase activity (87). Normally, Na-K-ATPase is the primary defense against the osmotic shifts caused by severe hyponatremia, and inhibition by estrogen makes the development of cerebral edema more likely. Estrogen may also lead to increased cerebral vasoconstriction in response to AVP leading to relative cerebral ischemia (87). Other factors that may increase the risk for fatal cerebral edema by impairing brain adaptation to cell volume changes include hypoxia and high vasopressin levels (86). Finally, decreased muscle mass in female individuals and lower body weight raise the risk for hyponatremia (59).

Treatment of severe, symptomatic hyponatremia likely will require intensive unit care with nephrologic or endocrinologic consultation. In those who have a negative free water clearance and an elevated urine osmolality at the time of presentation, administration of 0.9% sodium chloride or hypotonic fluids should be avoided and hypertonic 3% saline should be used. Furthermore, as described by Ayus *et al.* (77), in patients with symptomatic hyponatremic encephalopathy, 3% hypertonic saline should be used to increase the serum sodium rapidly. This therapy should be initiated as soon as possible after the diagnosis of hyponatremia is determined and should not be withheld in those with concomitant pulmonary edema (77). Analogous to those with exercise-associated hyponatremia, it could be argued that those who present with symptoms consistent with hyponatremic encephalopathy (seizures), 100 to 200 ml of 3% saline should be administered as soon as possible (88). This regimen should acutely raise the serum sodium concentration by 3 to 5 mEq/L, thereby reducing the degree of cerebral edema and relieving symptoms. There is clear benefit from this ap-

proach with little likelihood of harm, because the sodium load is only 51 mEq.

In most of the reported cases of ecstasy-induced hyponatremia, the sodium spontaneously and rapidly corrected either with little therapy or with fluid restriction. In those cases, AVP levels likely had fallen very quickly and a spontaneous free water diuresis had begun. Thus, patients with mild to moderate symptoms (*e.g.*, headache, dizziness, nausea and vomiting) should be treated with fluid restriction and observed until the onset of a spontaneous diuresis, which will correct the hyponatremia and lead to resolution of the symptoms. Intravenous isotonic saline is not necessary for most patients and may worsen the hyponatremia if the patient is euvoletic and has elevated AVP levels with a urine osmolality >300 mOsm/kg. Monitoring of urine output, serum sodium, and urine osmolality and sodium should be performed to allow identification of patients who may spontaneously develop an aquaresis once AVP levels fall or be more refractory and require 3% hypertonic saline.

Conclusions

Ecstasy use is associated with both the development of AKI and hyponatremia. Most of the episodes of AKI are due to pigment-induced acute tubular necrosis associated with rhabdomyolysis. More common, ecstasy can lead to severe and life-threatening hyponatremia. The pathogenesis of ecstasy-induced hyponatremia represents a “perfect storm” of drug-induced AVP secretion, drug-induced thirst, and the ready availability of fluids. Tragically, young people who take a single dose of ecstasy are at risk for this life-threatening complication. Awareness of the complications that are associated with ecstasy needs to be significantly heightened in an effort at prevention. Fluid ingestion should not be pushed to extremes, and ambient temperatures should be kept lower to decrease the risk for hyperthermia. Emergency personnel and physicians should be aware of ecstasy-related complications to decrease the potential mortality that is associated with this drug.

Disclosures

None.

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