

High incidence of mild hyponatraemia in females using ecstasy at a rave party

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ABSTRACT

Background. Globally, millions of subjects regularly use ecstasy, a drug popular due to its empathogenic and entactogenic effects. Dilutional hyponatraemia, mainly caused by direct stimulation of antidiuretic hormone (ADH) secretion by ecstasy, is among the many side effects of the drug (active substance 3, 4-methylenedioxymethamphetamine, MDMA). Severe, symptomatic hyponatraemia related to the use of MDMA has been reported in more than 30 cases. The mortality of this complication is high and mainly females are involved. Dramatic cases that reach the literature probably represent the tip of the iceberg. We decided to study the incidence of hyponatraemia in subjects using MDMA at an indoor rave party.

Methods. The study was performed at the indoor event 'Awakenings', held in Amsterdam in the fall of 2010. The plasma sodium concentration was measured at the party using a point of care method in 63 subjects using MDMA and 44 controls. The use of MDMA was confirmed by a urine test.

Results. The plasma sodium concentration in subjects using MDMA was significantly lower than in those not using the drug (138 ± 2 mmol/L versus 140 ± 2 mmol/L, respectively, $P < 0.001$). The overall incidence of hyponatraemia, defined as a plasma sodium concentration < 136 mmol/L, was 14.3% in MDMA users (9/63 subjects). Most cases of hyponatraemia occurred in females, in whom the incidence was 26.7% (8 of 30 females), with lowest values of 133 mmol/L. The number of ecstasy pills ingested by the females developing hyponatraemia was not different from that ingested by those who did not develop this complication. Fluid intake in ecstasy users exceeded that of non-users, suggesting a dipsogenic effect of the drug.

Conclusions. Only 3% of males, but no less than ~25% of females attending a rave party and using MDMA developed mild hyponatraemia during the event. Especially females are therefore probably also at risk of developing severe symptomatic hyponatraemia. Not using MDMA is obviously the best option to prevent MDMA-induced hyponatraemia. However, accepting the fact that millions use the drug every weekend, strategies should also be developed to prevent hyponatraemia in subjects choosing to take MDMA. This would include matching the electrolyte content of the fluids and food ingested to that of the fluids that are lost during the use of MDMA, mainly by perspiration. Users of MDMA and emergency health care workers should become more aware of the relatively high incidence of MDMA-induced hyponatraemia and of potential strategies to prevent this complication.

INTRODUCTION

Globally, millions of subjects regularly use ecstasy, which is popular due to its empathogenic and entactogenic effects. Hyponatraemia is among the many side effects of the drug that contains the active substance MDMA (3, 4-methylenedioxymethamphetamine). More than 30 cases of severe, symptomatic dilutional hyponatraemia related to the use of ecstasy have been reported [1–5]. In a retrospective analysis of symptomatic MDMA intoxications reported to the California Poison Control System in a 5-year time span, 73 additional cases of hyponatraemia (plasma sodium concentration < 130 mmol/L) were identified [6]. Symptoms, which include headache, altered mental status and seizures, are probably caused by cerebral oedema. There is a striking preponderance of

females presenting with this complication [6], which had a mortality of 50% in one case series [1]. The hyponatraemia is probably caused by MDMA-induced release of antidiuretic hormone (ADH) through a serotonergic pathway, combined with a high intake of hypotonic fluids. Other factors, including MDMA-induced polydipsia, solute loss in sweat and rapid re-absorption of hypotonic fluid accumulation in the intestines, may also play a role [1]. As suggested by Cherney *et al.* [7], it is likely that the cases of severe symptomatic hyponatraemia reported in the literature represent the tip of the iceberg, implying that less severe forms of hyponatraemia may occur in asymptomatic subjects using MDMA. The purpose of our study was to determine the incidence of hyponatraemia in a large group of unselected, asymptomatic subjects using MDMA at a rave party.

SUBJECTS AND METHODS

The study was performed at the indoor rave event 'Awakenings', held in Amsterdam on 8 and 9 October 2010. Visitors of this event were asked to participate in the study, which was approved by the Medical Ethical Board of the University Medical Centre Utrecht. Approximately 4000 people attended the rave party each night. The goal was to include around 50 MDMA users and 50 non-MDMA users (control group), with both sexes equally represented in the two groups. Visitors were addressed in the 'chill out' space of the event by drug educators experienced in recognizing users of different drugs, in particular those using MDMA. Participants were not selected on the basis of possible symptoms of hyponatraemia or other adverse effects of MDMA. After obtaining informed consent at a special research stand, the time of inclusion was noted and participants completed an anonymous questionnaire providing information on the type, dose and the time of intake of any drugs used. Information was also obtained on food and fluid intake. In addition, the time of arrival at the rave party, age, sex, body weight and height were recorded. Next, blood was obtained by finger prick and the concentrations of sodium (Na), potassium, haemoglobin and haematocrit were measured with a point of care measurement using the i-STAT Portable Clinical Analyser system (Abbott Point of Care Inc., 400 College Road East, Princeton, NJ 08540). Regarding sodium, this involves a direct sodium concentration measurement with a normal range specified by the clinical chemistry department of our institution of 136–146 mmol/L. Hyponatraemia was defined as a plasma sodium concentration of <136 mmol/L. Finally, MDMA usage was checked with a rapid urine drug test (Nal von Minden Drug Screen). The test is positive when the MDMA urine concentration is >500 ng/mL. It also detects MDA (3, 4-methylenedioxyamphetamine, >1.000 ng/mL), MDEA (3, 4-methylenedioxyethylamphetamine, >300 ng/mL) and PMA (paramethoxyamphetamine, >5000 ng/mL). All information was collected on data sheets that could not be traced to individual participants. To prevent legal consequences of illicit drug use for participants, the organizers of the event agreed that security surveillance would not be performed in the research stand area and that visitors to this area would not be addressed by security personnel.

STATISTICAL ANALYSIS

One-way analysis of variance with Bonferroni's protection for repeated measures was used to test for differences in the means. Whenever values were not distributed normally (e.g. fluid intake), non-parametric testing was performed (Mann-Whitney *U*-test). Data are reported as mean \pm SD, or as median and interquartile range when not distributed normally. A *P* value of <0.05 was considered to reflect statistical significance. A *Z*-test was used to compare proportions.

RESULTS

Participant characteristics

A total of 107 rave visitors participated in the study. Their mean age was 26 ± 6 years (range 17–52 years), and 54 (50.5%) were males. Urine samples for MDMA testing were obtained in 73 subjects (68.2%). In these subjects, questionnaires and urine tests were in agreement for MDMA use in all cases. Consequently, the questionnaire results were used to divide all 107 subjects over the MDMA user and non-user groups. According to the questionnaires, 63 subjects (58.9%) had used MDMA at the event. It is of note that the drug educators had difficulty in finding subjects who had not used MDMA towards the end of the party, which explains the overrepresentation of MDMA users in our sample. Body weight, height and body mass index were lower in females compared with males, but there were no differences in these variables according to the MDMA use status. Age was similar in males and females, both in MDMA users and non-users (Table 1).

Fluid intake

The estimated fluid intake derived from the questionnaires until the moment of blood sampling in subjects using MDMA was significantly greater than in non-users (2.0 ± 0.9 L, $n = 64$ versus 1.4 ± 0.7 L, $n = 41$, $P < 0.01$). The median and interquartile ranges were 1.9 L (1.4 L–2.5 L) and 1.2 L (1.0 L–2.0 L), respectively ($P < 0.01$). In males, fluid intake was 1.7 ± 0.8 L in those not taking MDMA and 2.2 ± 0.8 L in those using MDMA. In females, the corresponding figures were 1.2 ± 0.6 and 1.8 ± 0.9 L, respectively. When corrected for body weight or BMI, the gender difference in fluid intake disappeared, but MDMA users still had higher fluid intakes than subjects not taking MDMA.

MDMA use

The average number of MDMA tablets taken was 1.9 ± 0.8 in males and 1.4 ± 0.9 in females. Most subjects did not know the MDMA content of the pills they had taken. According to the yearly report of the National Drug Monitor, the mean MDMA content of ecstasy pills on the Dutch market in 2010 was 90 mg (30% of pills contained >105 mg, maximum 213 mg/pill) [8]. The mean time elapsed between the intake of MDMA and blood and urine sampling was 238 ± 130 min in males and 252 ± 104 min in females. Most subjects reported that they ingested MDMA at the party, which is confirmed by the time spent at the party of 309 ± 80 min and 298 ± 106 min for males and females,

Table 1. Participant characteristics

	Males		Females	
	No MDMA	MDMA	No MDMA	MDMA
Number (% of total)	21 (19.6%)	33 (30.8%)	23 (21.5%)	30 (28.0%)
Age (years)	26.0 ± 6.2	27.8 ± 7.1	24.7 ± 5.1	26.7 ± 5.6
Weight (kg)	78.5 ± 12.3	81.3 ± 11.5	62.8 ± 7.3 ^a	65.2 ± 8.7 ^b
Height (cm)	184 ± 6	186 ± 5	171 ± 6 ^a	172 ± 7 ^b
BMI	23.2 ± 3.3	23.4 ± 2.9	21.4 ± 2.0 ^a	21.9 ± 2.3 ^b
Time at event (min)	270 ± 104	309 ± 80	270 ± 186	298 ± 106
Time after MDMA Intake (min)	n.a.	238 ± 130	n.a.	252 ± 104
Number of pills	n.a.	1.9 ± 0.8	n.a.	1.4 ± 0.9
Estimated fluid intake (L)	1.7 ± 0.7	2.2 ± 0.8	1.2 ± 0.6	1.8 ± 1.0

Data are presented as mean ± SD.
^aFemales without MDMA versus males without MDMA, $P < 0.01$.
^bFemales using MDMA versus males using MDMA, $P < 0.01$.

respectively. Based solely on the questionnaires, other drugs were taken incidentally, including speed ($n = 14$), cocaine ($n = 9$), GHB ($n = 5$), THC ($n = 10$) and ketamine ($n = 1$).

Plasma sodium concentration

The mean plasma sodium concentration in MDMA users was 137.9 ± 2.2 mmol/L. This was significantly lower ($P < 0.001$) than the mean value of 140.1 ± 2.0 mmol/L in those not using MDMA. The mean plasma sodium concentration in males using MDMA (138.9 ± 2.0 mmol/L, range 135–143 mmol/L) was significantly lower than in male non-users (141 ± 2.0 mmol/L, range 137–145 mmol/L, $P < 0.001$). The lowest mean plasma sodium concentration was observed in female MDMA users (136.9 ± 2.0 mmol/L, range 133–140 mmol/L), which was significantly lower than in females not using the drug (139.3 ± 1.8 mmol, range 136–142 mmol/L, $P < 0.001$). Interestingly, the plasma sodium concentration in females not using MDMA was also significantly lower than in male non-users ($P < 0.001$) (Table 2, Figure 1).

The overall incidence of hyponatraemia, defined as a plasma sodium concentration of <136 mmol/L, in subjects using MDMA was 9 of 63 (14.3%), as opposed to zero in participants not taking the drug. In males using MDMA, a plasma sodium concentration of <136 mmol/L was observed in only one of the 33 subjects (3.0%), whereas this occurred in 8 of 30 females (26.7%) using MDMA ($P = 0.02$). In the latter group, the plasma sodium concentrations were 133 mmol/L ($n = 2$), 134 mmol/L ($n = 1$) and 135 mmol/L ($n = 5$), respectively. The eight females that became hyponatraemic after MDMA intake did not differ from the 22 females using MDMA without hyponatraemia (plasma sodium concentration 134 ± 0.9 mmol/L versus 138 ± 1.4 mmol/L, $P < 0.05$) with respect to body mass index (21.5 ± 2.0 versus 22.1 ± 2.4 , NS), fluid intake (1.9 ± 1.0 l versus 1.7 ± 1.0 l, NS) or the number of ecstasy pills ingested (1.1 ± 0.2 versus 1.6 ± 1.1 , NS).

Plasma potassium and haemoglobin concentrations and haematocrit

The mean plasma potassium concentrations were within the normal range and did not differ in the four groups. Mean plasma haemoglobin and haematocrit were not different according to the MDMA use status, although, as expected, lower in females compared with males (Table 2).

DISCUSSION

This is the first study exploring the incidence of hyponatraemia in a large group of MDMA users at an actual rave party. Overall, the incidence of mild hyponatraemia in MDMA users was 14.3%, but the incidence differed markedly in females (27.3%) as opposed to males (3.0%). The mean plasma sodium concentration was significantly lower in subjects using MDMA (137.9 ± 2.2 mmol/L) than in those not using the drug (140.1 ± 2.0 mmol/L). Our findings support the suggestion that severe, symptomatic hyponatraemia is likely to be the extreme part of a spectrum of different degrees of hyponatraemia that may be induced by MDMA [7].

The pathogenesis of MDMA-associated hyponatraemia is multifactorial [1]. Several studies have shown that MDMA or its metabolites stimulate ADH secretion through serotonergic pathways [9, 10]. Loss of hypotonic fluids through exercise and heat-induced perspiration is the primary disturbance in volume balance in visitors of rave parties. Notably, hypotonic fluid losses *per se* will induce a state of hypernatraemia. The intake of large volumes of fluid hypotonic to sweat, which are subsequently retained because of MDMA-induced ADH excess, is a prerequisite for hyponatraemia to develop. In our study, the fluid intake up to the moment of blood testing reported in the questionnaires was significantly greater in subjects using MDMA. This may have been due to the advice given specifically to MDMA users to drink plenty of fluids to

Table 2. Laboratory results

	Males		Females	
	No MDMA	MDMA	No MDMA	MDMA
	(A)	(B)	(C)	(D)
Plasma Na (mmol/L)	141.1 ± 2.0	138.9 ± 2.0 ^a	139.3 ± 1.8 ^b	136.9 ± 2.0 ^{cd}
Plasma K (mmol/L)	4.5 ± 0.6	4.3 ± 0.4	4.2 ± 0.5	4.3 ± 0.5
Haemoglobin (mmol/L)	9.9 ± 0.6	9.9 ± 0.5	8.9 ± 0.6 ^e	8.9 ± 0.6 ^f
Haematocrit	0.47 ± 0.03	0.50 ± 0.17	0.42 ± 0.03 ^e	0.42 ± 0.03 ^f

Data are presented as mean ± SD.

^aMales using MDMA versus males not using MDMA, $P < 0.01$.

^bFemales not using MDMA versus males not using MDMA, $P < 0.01$.

^cFemales using MDMA versus females not using MDMA, $P < 0.01$.

^dFemales using MDMA versus males using MDMA, $P, 0.01$.

^eFemales without MDMA versus males without MDMA, $P < 0.01$.

^fFemales using MDMA versus males using MDMA, $P < 0.01$.

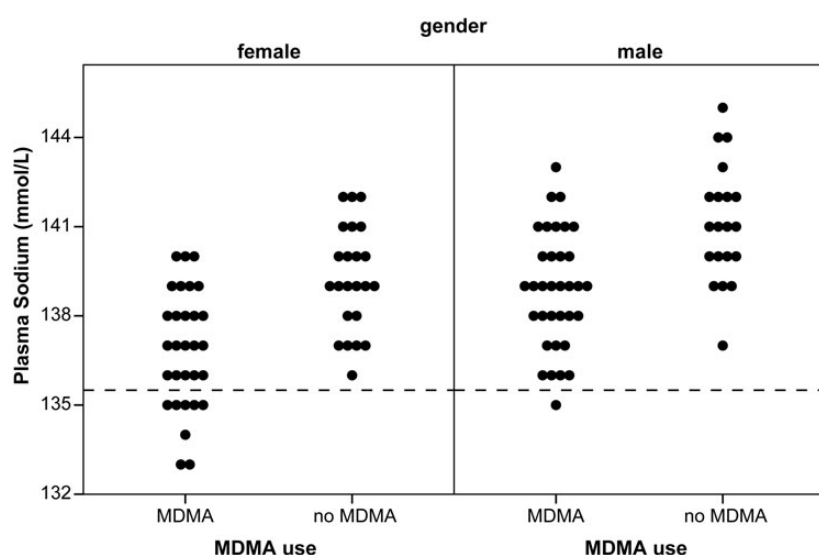


FIGURE 1: Plasma sodium concentration of all participants. The plasma sodium concentration of female MDMA users (136.9 ± 2.0 mmol/L, range 133–140 mmol/L) is significantly lower than in females not using MDMA (139.3 ± 1.8 mmol/L, range 136–142 mmol/L, $P < 0.001$). The mean plasma concentration in males using MDMA (138.9 ± 2.0 mmol/L, range 135–143 mmol/L) is significantly lower than in male non-users (141 ± 2.0 mmol/L, range 137–145 mmol/L, $P < 0.001$)

prevent MDMA-induced hyperpyrexia [1]. However, subjects given MDMA in a controlled research setting also drink more water compared with control subjects, suggesting a primary dipsogenic effect of the drug [11]. In agreement with this, saliva levels of MDMA are positively associated with feeling thirsty [12]. Consequently, as suggested by others [13], MDMA-induced polydipsia may be a factor contributing to the development of hyponatraemia.

Our study confirms that females are more prone to develop MDMA-induced hyponatraemia. In 188 cases of ecstasy intoxication reported to the California Poison Control System with a known plasma sodium concentration, the odds ratio of having a plasma concentration <130 mmol/L for women compared with men was 3.97 [6]. Furthermore, almost 90% of the cases of

symptomatic hyponatraemia reported in case series concerned females [1–5, 14]. The predisposition for females to develop hyponatraemia during the use of MDMA is probably multifactorial. First, females seem to be more susceptible to the effect of MDMA on ADH secretion. Simmler *et al.* recently showed that MDMA increases plasma copeptin in females but not in males [11]. Copeptin is the C-terminal part of the ADH precursor ‘preprovasopressin’ which is produced in an equimolar ratio to ADH. Unlike ADH, it is a stable peptide that can be measured more reliably than ADH [15]. Females also appear more susceptible to other serotonergic effects of MDMA, as they report more thirst and the sensation of a dry mouth after MDMA exposure [16]. It is of note that the number of ecstasy pills ingested by the females that developed hyponatraemia after

MDMA intake was not greater than in those who did not. Differences in MDMA metabolism or in the pituitary sensitivity to the ADH secreting effect of MDMA or its metabolites, perhaps related to the phase of the menstrual cycle, could explain this individual tendency to develop hyponatraemia after doses of MDMA not considered to be excessive.

The relatively mild hyponatraemia observed in the females in our study explains their lack of recognizable symptoms. Neurological symptoms of acute hyponatraemia depend in part on the severity of hyponatraemia. Nausea and malaise occur at plasma sodium concentrations <125 mmol/L. At values between 120 and 115 mmol/L, headache and reduced levels of consciousness occur, whereas severe symptoms such as coma and seizures develop at values <115 mmol/L [17]. As discussed below, however, Ayus *et al.* have shown that gender is a key determinant of symptoms in hyponatraemia, females becoming much more symptomatic than males at similar levels of hyponatraemia [18]. The specific presentation of hyponatraemia with severe non-cardiogenic pulmonary oedema reported in females with hyponatraemia due to other causes [19, 20] has also been observed in subjects with MDMA-induced hyponatraemia. In the literature, this is known as the Ayus-Arieff syndrome, and the failure to recognize and treat with hypertonic saline usually results in death [21].

An intriguing observation is that the mean plasma sodium concentration in females not using MDMA at the rave party was significantly lower than in males not taking the drug, although there were no frank cases of hyponatraemia in these females. Due to the design of the study, the plasma sodium concentrations at entry are not known, and it cannot be excluded that the initial values in females were already lower than in males. Although the plasma sodium concentration appears to be slightly lower in females in the luteal phase compared with males [22], there is no gender specific normal range for the plasma sodium concentration in females not stratified for the phase of the luteal cycle and males [23]. Consequently, it is possible that exercise and stress-induced ADH secretion combined with intake of hypotonic fluids [24] caused the reduction in plasma sodium concentration in female ravers not using MDMA. In this respect, the situation may be similar to the hyponatraemia induced by long distance running, which also occurs more frequently in females than males and may have a similar pathophysiology [25].

Our results confirm the general tendency of females to be more susceptible to develop hyponatraemia than males. This has been demonstrated for hyponatraemia induced by exercise [25] or caused by drugs such as anti-epileptics, antidepressants and thiazides [26]. In humans, estrogens, but not progesterone, stimulate ADH secretion [27]. Estrogens also induce a shift in the osmotic regulation of ADH and thirst, resulting in a lower operating point for plasma osmolarity, which predisposes females to develop hyponatraemia [28]. Finally, studies involving hypertonic saline infusion have suggested greater renal ADH sensitivity in females than males [22]. In accordance with this, desmopressin induces a larger antidiuretic response and causes more hyponatraemia in females [29]. Studies in rats suggest that this may be due to an increased expression of the renal vasopressin receptor in females [30].

Importantly, hyponatraemic females are not only more prone to develop symptoms than males, but they also have a much

worse outcome. In menstruant females with postoperative hyponatraemia-induced encephalopathy, the risk of death or permanent brain damage was increased ~25-fold compared with males or post-menopausal females [18]. Other causes of hyponatraemia have a similar poor outcome [19, 31]. This is also true for MDMA-induced hyponatraemia, as women with hyponatraemia have a roughly 4-fold increased risk of developing coma compared with those without hyponatraemia, while this risk was not increased in hyponatraemic males [6]. As reviewed by Ayus *et al.*, the increased sensitivity of the female brain to hyponatraemia is caused by insufficient brain cell volume regulation in hyposmolar states, which is at least partly estrogen-related [32].

Our study was carried out at an actual rave party in unselected subjects and therefore, reflects real-life events. A study like this may be feasible only in a country like the Netherlands where the attitude towards the use of drugs is relatively tolerant and is aimed at the detection, treatment and prevention of adverse side effects [33]. This attitude, implemented by both the organizers and the security personnel, made it possible to perform this study without the risk of legal consequences for the participants. In this respect, our study differs from that by Wolff *et al.* [34] who studied 30 subjects before and after visiting a party in a study facility outside the party location. In subjects who had used MDMA, ($n = 17$), the plasma sodium concentration fell from 137.7 ± 0.5 to 135.9 ± 0.4 mmol/L, but remained unchanged in those not using the drug ($n = 13$). The incidence of hyponatraemia in MDMA users in this study of 17.6% agrees very well with our figure of 14.3%.

The implications of our findings remain to be determined. Although our study suggests that ~25% of females using MDMA develop asymptomatic hyponatraemia, only ~30 individual cases of severe, symptomatic hyponatraemia have been reported since 1993. As the estimated number of MDMA users ranges between 10.5 and 25.8 million worldwide [35], this would suggest that most MDMA users with mild hyponatraemia do not progress to more severe forms of hyponatraemia. However, the lack of more reports of severe MDMA-induced hyponatraemia could be due to the perception that the likelihood of publishing yet another case in a high impact journal is small. Alternatively, it is also possible that cases of more severe, both non-lethal and lethal symptomatic hyponatraemia go unnoticed because they develop after leaving rave parties. Several case histories suggest that this may indeed be the case [2, 21]. The continuing presence of MDMA or its metabolites [36] and ongoing ADH release, possibly combined with the late sudden reabsorption of hypotonic fluid accumulated in the intestines [7], may cause such delayed onset of severe hyponatraemia. In this respect, it is of note that the interval between the intake of MDMA and the plasma sodium measurement in our study was only 4 h, and the mean estimated fluid intake up to that point was only 2 L. It is, therefore, conceivable that both the incidence and severity of hyponatraemia would increase when studying subjects longer after the party.

Our findings indicate that MDMA users and emergency health care workers should be aware of hyponatraemia as a complication of MDMA use. Preventive measures should be considered to avoid MDMA-induced hyponatraemia, specifically in females, who tend to develop hyponatraemia even at 'normal' dosages of MDMA at relatively limited fluid intakes.

Obviously, not using MDMA is the best way to avoid this complication, but in view of the huge number of subjects using MDMA, discouraging the use of MDMA to prevent hyponatraemia is not a realistic option. Hyponatraemia could be prevented if the fluid replacing the sweat losses would be roughly isotonic to sweat with respect to electrolyte osmoles. As the sweat sodium concentration is 50–60 mmol/L, most sports drinks, with a sodium concentration of ~20 mmol/L for palatability reasons, are not suitable for this purpose [37]. Dilutions of commercially available broths or soups with a high sodium content could serve this purpose [38], although installing a soup bar in the chill out space of a rave party may not be considered ‘very cool’. Alternatively, one can design protocols that discourage the drinking of large volumes of hypotonic fluid and combine the intake of sports drinks with foods resulting in a net isotonic intake of electrolyte osmoles and water. Further studies should determine whether such measures can reduce the high incidence of hyponatraemia after the use of MDMA as observed in the current study.

CONFLICT OF INTEREST STATEMENT

None declared.

(See related article by Moritz *et al.* Ecstasy-associated hyponatremia: why are women at risk? *Nephrol Dial Transplant* 2013; 28: 2206–2209.)

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Laboratory aspects of circulating α -Klotho

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ABSTRACT

Background. α -Klotho is a protein mainly produced in the kidney. Its circulating form has been suggested to link renal

damage and distant tissue pathology. As three assays to measure α -Klotho became commercially available, we performed an evaluation of these commercially available Klotho assays.

Methods. We studied within-run variation, between-run variation, matrix effects, linearity, and recovery of added