Q J Med 2002; **95**:475–483

Masterclasses in medicine

QJM

Acute hyponatraemia and 'ecstasy': insights from a quantitative and integrative analysis

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Summary

A 20-year-old woman attended a 'rave party' where she took the drug 3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy'). She had used this drug previously without serious adverse effects. On this occasion, while both she and her friends drank a large quantity of water, only she became seriously ill. The initial manifestation was an altered sensorium; several hours later she had a *grand mal* seizure. In the Emergency Department, the most striking features were the severe degree of hyponatraemia (112 mmol/l) and cerebral oedema. To explain the basis for this life-threatening clinical presentation, an imaginary consultation was sought with Professor McCance. Using both a deductive and a quantitative analysis that involved several medical subspecialties, he illustrated that a simple story of water ingestion and vasopressin release was not sufficient to explain her hyponatraemia. It was only after events in her gastrointestinal tract were analysed that a plausible hypothesis could be constructed.

Introduction

This is the third article in our series on the application of principles of integrative physiology that begins at the bedside with a problem in the fluid, electrolyte, acid-base, and/or energy-metabolism area.[1,2] Once again, our consultant is Professor McCance, an integrative physiologist who practiced medicine more than 50 years ago. Although he uses information that was primarily present during his lifetime, McCance often seeks information from both consultants in his era, and from today's physicians who have a background in molecular medicine. Using all of this information, the disturbed physiology in this patient can be better understood. His focus is on concepts—additional data are sought only when necessary. He relies on a quantitative analysis based on whole-body physiology to formulate a broad-based differential diagnosis and a specific plan for therapy.

The consultation

Because of his interest in patients with abnormalities in the salt and water area, the housestaff told Professor McCance about a thin 20-year-old

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woman (weight 50 kg) who was brought to the Emergency Department last week. Her story was not unusual. The night prior to admission, this healthy woman attended a 'rave party' where she took one tablet of 3,4-methylenedioxy-methamphetamine (MDMA, 'ecstasy'). She had taken the drug before without ill effects. Like other attendees at the event, she also drank a large volume of water to avoid 'dehydration' because of profuse sweating due to dancing in a hot environment. Unlike the previous occasions, she became drowsy, had a headache and felt unwell 6 h after arriving at the party. She was advised to lie down in a quiet room. Three hours later, she had a *grand mal* seizure and was brought promptly to hospital. Suspecting that the basis of the seizure was acute hyponatraemia, blood was drawn and to nobody's surprise, her plasma sodium (Na^+) concentration (P_{Na}) was 112 mmol/l. Given the long time interval and water permeability in capillaries and cell membranes, her P_{Na} probably represented a near-equilibrium condition after water distribution across body fluid compartments. Therapy was instituted to decrease her brain cell size (hypertonic saline was given) to minimize the risk of coning. Recovery was uneventful.

When asked, the housestaff said the reason for her acute hyponatraemia was obvious—a water surplus due to the ingestion of a large volume of water in a setting where vasopressin acts. Professor McCance was not so sure—he felt that the explanation for her acute fall in P_{Na} would only become clear after a quantitative analysis. To make these calculations, two assumptions were required. First, that the patient had a normal P_{Na} (140 mmol/l) before the acute episode. Second, that because she was thin, her total body water (TBW) would be close to 60% of body weight—30 l. As always, our Professor began his analysis with the application of principles of physiology (Table 1).

Physiology principle 1: The P_{Na} is the ratio of Na^+/water in the ECF compartment

The P_{Na} will fall if there is a deficit of Na^+ and/or a gain of water in the extracellular fluid (ECF) compartment.

Return to the bedside: Because blood was drawn a considerable time after the seizure occurred, the housestaff did not think it likely that there was an error in her P_{Na} due to a transient shift of water into cells secondary to a sudden rise in ICF osmoles during a seizure.[3]

Professor McCance began his analysis by calculating the deficit of Na^+ needed to cause the observed fall in her P_{Na}. To perform this calculation, he emphasized that water moves across cell membranes rapidly and achieves osmotic equilibrium. As soon as Na^+ is removed from the ECF compartment, its effective osmolality will fall, and water will enter cells. It is for this reason that TBW rather than ECF volume is used to calculate the deficit of Na^+.[4] Hence to lower her P_{Na} by 28 mmol/l, her Na^+ deficit would need to be 840 mmol (28 mmol/l×TBW of 30 l). Professor McCance's next step was to consider the possible routes for Na^+ loss. He conceded that while some Na^+ could be lost in the urine, the obvious site for a major loss of Na^+ was sweat. *'What is the expected impact of a loss of sweat on the P_{Na}?'*, he asked.

Table 1 Summary of physiology principles

Physiology principle	Comment
1. The P_{Na} is the ratio of Na^+/water in the ECF compartment	Hyponatraemia may be due to a loss of Na^+ and/or an excess of EFW
2. Evaporation of water in sweat is needed for heat dissipation	Sweat loss in humans can be 1–2 l/h
3. Sweat is a hypotonic fluid because Na^+ and Cl^- are largely reabsorbed in the ducts of sweat glands	The usual sweat [Na^+] in normal individuals is ~15–40 mmol/l
4. Hyponatraemia may develop when there is an intake of EFW and vasopressin to prevent its renal excretion	Both a source of vasopressin and EFW are needed to develop and sustain hyponatraemia
5. Thirst is stimulated primarily when there is a high P_{Na}	Other thirst stimuli are poorly understood, such as in the case of primary polydypsia
6. Absorption of nutrients in the GI tract is coupled to Na^+ absorption	Humans must secrete more than their total ECF Na content (1400 mmol) each day to absorb dietary nutrients
7. Loss of muscle mass causes a greater degree of hyponatraemia when EFW is retained	More water enters brain cells in thin, cachectic individuals when EFW is retained

EFW, electrolyte-free water.

Question 1: What is the expected impact of a loss of sweat on the P_{Na}?

Professor McCance was the ideal person to ask this question, because he had conducted important research in this very area, and published the landmark article in 1936.[5]

Physiology principle 2: Evaporation of water in sweat is needed for heat dissipation

Because heat loss must be large with intense activity in a warm environment, sweat volume should be large. When 1 l of water evaporates, ~500 kcal are dissipated.[6] As an experimental subject in his own study, recounted McCance, he lost close to 2 l of sweat per hour in a hot environment.[5]

To defend against an excessive degree of contraction of the ECF volume, the water in sweat should be derived from TBW. In order to explain how sweat originates from TBW, the process of sweat formation was reviewed. The first step is the active secretion of Na^+ and chloride (Cl^-) at the base (coil) of the sweat gland (Figure 1). This segment must have open water channels so that water enters the lumen of the sweat gland, making this an isotonic saline solution. Upstream in the sweat duct, Na^+ and Cl^- are reabsorbed, but the duct epithelium of the sweat gland must be impermeable to water permit the development of a very hyponatric luminal fluid to be used for evaporative heat loss.

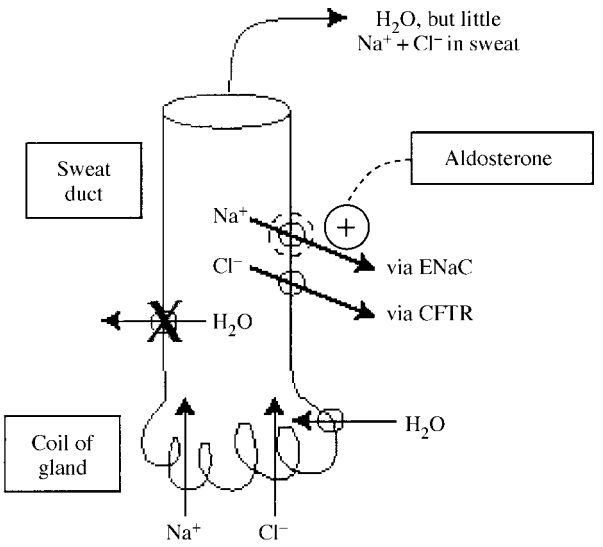

Figure 1. Formation of sweat. Sweat is formed in the coil of the sweat gland. The first step is the secretion of Na^+ with Cl^- in a water-permeable section of the gland. The second step is the reabsorption of Na^+ (via ENaC) and Cl^- (via CFTR) in the water-impermeable duct of the sweat gland. The third step is the evaporation of hypotonic fluid delivered to the surface of the skin for heat loss.

Return to the bedside: Because sweat losses are hypotonic, if sweating was the sole perturbation, it should cause the P_{Na} to rise. Notwithstanding, Professor McCance emphasized that one needs to examine balances, not simply inputs or outputs.[7] If, as was possible in our case, sweat loss was accompanied by the ingestion of an identical volume of electrolyte-free water (EFW), the P_{Na} could fall due to the net loss of Na^+.

The next step was to perform a quantitative analysis. If the usual Na^+ concentration in sweat is close to 30 mmol/l,[8,9] our patient would need a sweat volume (and a water intake) of 28 l to produce a negative balance of 840 mmol of Na^+ and develop a P_{Na} of 112 mmol/l. This simple calculation seemed to rule out the possibility of hyponatraemia due to a deficit of Na^+ from sweating, due to the low likelihood of our patient being able to lose 28 l of sweat and drink 28 l of water over the duration of the party. Our Professor then asked, *'Is it possible to have a large loss of Na^+ in a smaller volume of sweat?'*

Question 2: Is it possible to have a large loss of Na^+ in a smaller volume of sweat?

Physiology principle 3: Sweat is a hypotonic fluid because its Na^+ and Cl^- are largely reabsorbed in the ducts of sweat glands

The Renal Fellow added some new molecular insights (Figure 1). Na^+ is reabsorbed by an epithelial Na^+ channel (ENaC) while Cl^- is reabsorbed by a Cl^- ion channel. ENaCs are open and Na^+ absorption increases when aldosterone levels are elevated, while the Cl^- channels (cystic fibrosis transmembrane conductance regulator, CFTR) are defective, and Cl^- absorption decreased, in patients with cystic fibrosis (CF).

Return to the bedside: If the patient was normal before this acute illness, Professor McCance doubted that she had aldosterone deficiency due to adrenal insufficiency. On the other hand, she may have had an unrecognized defect in her CFTR if she had a very mild form of CF[10] or if the MDMA led to an inhibition of CFTR. Symptoms would now be restricted to times when there was excessive sweating. Nevertheless, he doubted that CF was present, but measurement of the patient's sweat Cl^- concentration (and molecular studies) could be done at a later time if this diagnosis was still a possibility. If MDMA blocked Cl^- channels, many more people would have this unusual complication of acute hyponatraemia.

Because all the explanations that centered on Na^+ loss seemed unlikely, a surplus of water was then examined as the mechanism that caused her hyponatraemia.

Physiology principle 4: Hyponatraemia will develop when there is an intake of EFW and vasopressin to prevent its renal excretion

Professor McCance chose to begin with the physiology of vasopressin[11] and asked, '*What stimulus is the most likely cause of vasopressin release in this patient*?'

Question 3: What stimulus is the most likely cause of vasopressin release in this patient?

In the face of hyponatraemia, vasopressin should not be released. Our team knew that vasopressin was present in their patient, because she had a urine osmolality (U_{osm}) that was five-fold higher than anticipated (256 mOsm/kg H_2O vs. the expected 50–60 mOsm/kg H_2O when vasopressin is absent). Professor McCance asked, 'Is there information to suggest that MDMA can cause the central release of vasopressin?'

The Senior Registrar responded that there was a recent study that addressed this issue.[12] Vasopressin levels rose when MDMA was ingested by normal subjects, and this effect lasted for many hours. Nevertheless, increased vasopressin levels will not cause a fall in the P_{Na} unless there is a source of EFW. In our patient, there was an obvious source of EFW, because partygoers are encouraged to drink large volumes of water to avoid the potential side-effects of MDMA.[13] One of the housestaff asked, *'Exactly how much water needs to be ingested to cause her P_{Na} to fall to 112 mmol?'*

Question 4: Exactly how much water must be ingested to cause her P_{Na} to fall to 112 mmol?

Because her P_{Na} declined acutely by 20% to 112 mmol/l, her TBW should be expanded by close to 20% or 6 l in this 50 kg woman. Therefore she would have had to drink and retain at least 6 l of EFW in approximately 9 h. In fact, this is an underestimate because she was dancing and therefore sweating in this hot environment. Even if she were to have lost only 0.5 l of sweat per hour over 9 h, she would have had to replace those losses, obligating her to drink another 3.5 l of pure water (4/5 of sweat is EFW) over the 9-h period, for a total oral intake of close to 10 l (i.e. >1 l/h).

Professor McCance was a strong advocate of learning by self-experimentation.[5] He put a challenge to the housestaff, because he suspected that drinking this much water in so short a time would prove to be a very difficult task. An experiment was devised to assess whether normal subjects would voluntarily drink 20 ml/kg over 30–60 min, a volume that is 1/6 of the required positive water balance for our patient to lower her P_{Na} to 112 mmol/l.

Fourteen normal volunteers, including Professor McCance drank 20 ml of water per kg body weight over 30–60 min; this is the volume consumed during the standard clinical water load test.[14] Thirst was assessed on a visual five-point scale. Every subject was unwilling to drink a larger volume of water because of the complete absence of thirst, a powerful aversion to further water ingestion, a feeling of bloating, and a variety of non-specific symptoms that included malaise, headache, and nausea. Professor McCance concluded that if normal subjects could only manage to drink 10% of the required EFW positive balance to achieve a P_{Na} of 112 mmol/l, the simple water-load theory, which appeared to be so obvious initially, now seemed unattractive because of the reluctance of volunteers to drink more water. Therefore he asked, *'What might have permitted our patient to overcome her aversion to drinking more water?'*

Question 5: What might have permitted our patient to overcome her aversion to drinking more water?

Physiology principle 5: Thirst is stimulated primarily when there is a rise in the P_{Na}

Water ingestion may be augmented due to both thirst stimulated by a $P_{Na} > 140$ mmol/l and to non-thirst stimuli such as habit, dry mouth, and/or hypovolaemia.

Return to the bedside: The housestaff had established that normal subjects would not ingest enough water to cause the needed positive balance of EFW to lower their P_{Na} to a dangerously low range. Perhaps a mood-altering drug such as MDMA might stimulate thirst and cause primary polydipsia. If MDMA in some way also inhibited sweating, it would reduce the amount of EFW needed to cause the hyponatraemia.

In summary, so far Professor McCance was confident that the cerebral oedema and the seizure were probably due to brain cell swelling, the result of a very low P_{Na}. His quantitative analysis left him very uncomfortable about the basis for her acute, severe hyponatraemia. Even the combination of

a huge volume of water intake along with some Na^+ loss in sweat seemed unlikely. He was reluctant to believe that water in her circulation failed to distribute rapidly in her ECF and ICF compartments in her major organs. He called for help, seeking the expertise of Horace Davenport, an eminent gastrointestinal (GI) physiologist. This simple admission of a need for help with the GI physiology did not go unnoticed by the housestaff. Dr Davenport was asked, *'Can the body lose hypertonic Na^+ via the GI tract?'*

Question 6: Can the body lose hypertonic Na^+ via the GI tract?

Physiology principle 6: absorption of nutrients in the GI tract

The absorption of glucose and amino acids across the luminal cell membrane is by co-transport with Na^+, using the low intracellular fluid Na^+ concentration created by the Na-K-ATPase located in their basolateral membranes (Figure 2)[15] as the driving force. The lumen needs to have a minimum of 1 luminal Na^+ per absorbable nutrient. The total number of glucose plus amino acids absorbed per day in a 50-kg adult is close to 2000 mmol. Because the diet provides close to 150 mmol of Na^+, normal individuals such as our patient must secrete more than the total quantity of ECF Na^+ (her ECF Na^+ content is 1400 mmol) each day into the lumen of the GI tract to absorb these dietary nutrients. The vast majority of these Na^+ ions enter the lumen in a passive fashion by diffusing between mucosal cells.[16] They do not enter the bulk phase of the luminal fluid, because as Na^+ ions diffuse into the unstirred layer, they are quickly reabsorbed.

Professor Davenport then commented on the concentration of Na^+ at the tip of the intestinal villi; this P_{Na} value is considerably higher than in the plasma of arterial blood.[16] The idea was that an intestinal villus behaved as if it had a countercurrent exchanger like the loop of Henle (LOH) (Figure 3). Moreover, the Na^+ absorbed from the diet and upper GI secretions is added in hypertonic form to the interstitial compartment at the tip of the villus which represents the bottom of its capillary loop. This hypertonicity persisted because of countercurrent exchange in the blood vessels in the villus.

Return to the bedside: Professor McCance thanked Professor Davenport for providing these fascinating insights to reveal how Na^+ could be lost into the lumen of the GI tract. He added that if GI motility was slow, and the lumen of the GI tract contained a large static volume of EFW, there could be net diffusion of Na^+ from the body into this luminal fluid.[17,18] Therefore there would be two ways to explain the GI contribution to hyponatraemia: (i) an initial, transient total body Na^+ deficit due to secretion of Na^+ into a fluid-filled GI lumen; and (ii) later there could be a total body EFW excess when this luminal EFW (plus Na^+ that entered the lumen by diffusion) was totally absorbed.

Given the slow process of diffusion in the bulk phase of the GI tract lumen, the degree of hyponatraemia might become progressively more severe even after water intake had been curtailed. These insights provided a clue to the natural history of this disorder—one cannot predict how much more the P_{Na} will fall over time due to ongoing EFW absorption and/or Na^+ loss, or how fast the rate of

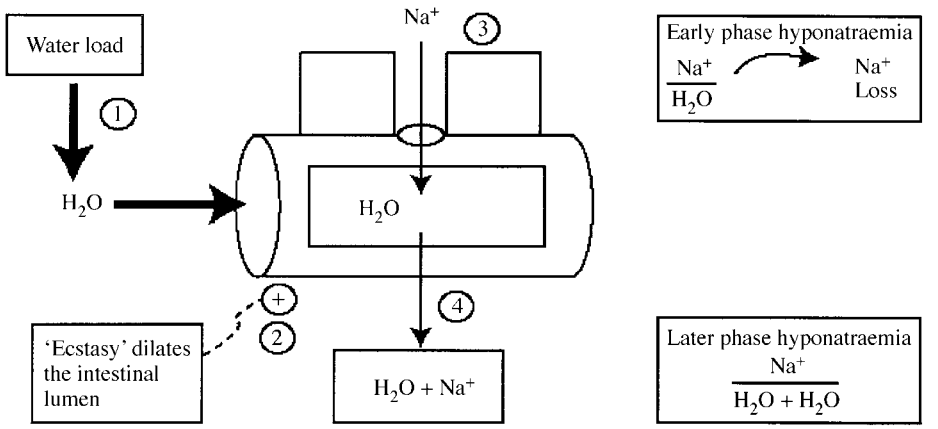

Figure 2. Role of the GI tract in hyponatraemia due to water ingestion. The first event is water ingestion (step 1). An unknown volume of water remains in the lumen of a dilated GI tract (step 2). Na^+ diffuses from the body into the lumen of the GI tract (step 3). This is aided by a high local Na^+ concentration (see Figure 3) and paracellular permeability for Na^+. The P_{Na} falls and the ECF volume is contracted at this stage. Later, when GI motility improves, the water plus Na^+ in the lumen is absorbed and causes a low P_{Na} due to an EFW gain (step 4).

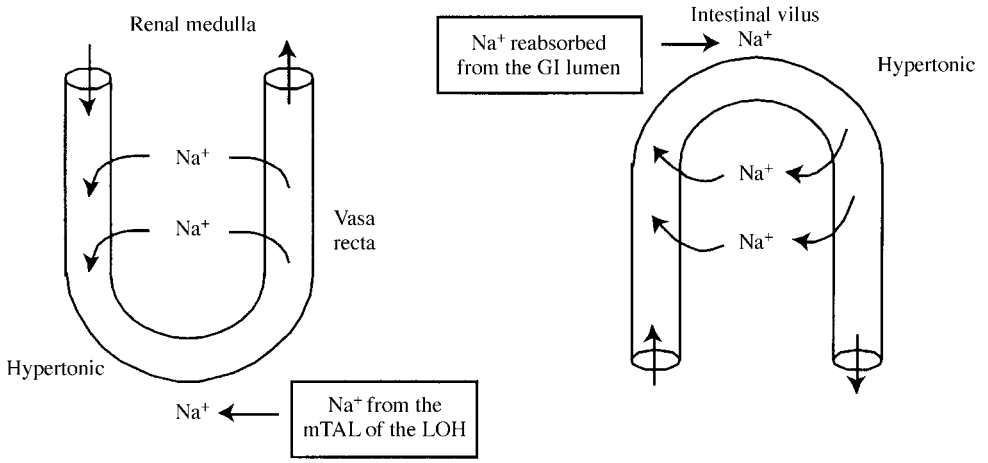

Figure 3. Generation of a high Na^+ concentration in the body. The hairpin-like structure represents a blood vessel that acts as a countercurrent exchanger—the vasa recta of the renal medulla (left) and the blood flow through an intestinal vilus (right). Na^+ is added without water near the bend of the loop in both structures as indicated by the rectangles. The net result is the maintenance of hypertonic saline in this area. This high Na^+ concentration is needed for EFW reabsorption from neighbouring water-permeable nephron segments in the kidney and to aid diffusion of Na^+ into the lumen in the intestinal tract.

change will be. Therefore as soon as MDMA users have even mild symptoms suggestive of acute hyponatraemia, they require careful clinical and laboratory monitoring to prevent complications secondary to a further fall in P_{Na}.[19,20] The common practice of leaving them to rest in a quiet area may place them at great risk.

The housestaff were amazed at how many new insights could be provided by a quantitative analysis of an 'obvious diagnosis'. Nevertheless, they still had one more question. *'Could the lumen of the intestinal tract accommodate enough water to account for the estimated Na^+ loss?'*

Question 7: Could the lumen of the intestinal tract accommodate enough water to account for the estimated Na^+ loss?

For loss of Na^+ into the lumen of the GI tract to be the *sole* cause of her hyponatraemia, 7 l of water containing 112 mmol/l Na^+ would be needed to achieve a Na^+ deficit of 840 mmol by this route, but was this possible? Professor McCance again used a simple calculation—the volume of a cylinder is $\pi r^2 h$. Using a radius of 1 or 2 cm and a length of 400 cm, the luminal volumes would be close to 1.2 and 4.8 l, respectively. Therefore, if active ingredients in 'Ecstasy' led to a degree of ileus with a 2 cm radius, a 7-litre water intake and its retention in the lumen of the stomach and small intestine could lead to the observed degree of hyponatraemia (Figure 3). Moreover, the sweat volume decreases when the ECF volume declines,[21] requiring less EFW ingestion to replace sweat losses. This combination of lesions could help to explain the pathophysiology of her hyponatraemia.

Professor McCance had not yet completed his analysis. He had suggested several possible routes of Na^+ loss, including sweat and loss into the lumen of the tract. Bearing in mind that she had to lose 840 mmol of Na^+ and that the Na^+ content determines the ECF volume, McCance asked the housestaff if the patient had any objective evidence of haemodynamic compromise. Our Professor reminded those present about his self-experimentation in 1936.[5] The conditions in that classical experiment were not unlike those in our patient. He (and two colleagues) induced severe Na^+ depletion by sweating 1–2 l per day and eating a NaCl-free diet. They had a deficit of Na^+ that was close to 1000 mmol over many days, yet they did not have a tachycardia or a fall in blood pressure. The only evidence consistent with altered haemodynamics was that Professor McCance experienced chest pain with exertion, which he had never had prior to the NaCl depletion experiment. His colleagues did not have chest pains despite a similar deficit of NaCl. He developed hyponatraemia, with a P_{Na} fall of 15 mmol/l. He asked *'How is it possible to lose half of the ECF Na^+ content and not compromise haemodynamics appreciably?'*

Question 8: How is it possible to lose half of the ECF Na^+ content and not compromise haemodynamics appreciably?

The housestaff were reluctant to accept that a deficit of 1000 mmol of Na^+ could be tolerated without

a haemodynamic collapse, because this was inconsistent with what they had been taught in medical school. The senior registrar reminded them that the data were clear and the investigator was both reliable and careful. An explanation for the absence of haemodynamic shock was therefore required. Going back to first principles of Starling forces, they outlined the variables that could defend the vascular volume despite the very large deficit of Na^+. First, there could be a larger than expected blood volume. Second, there are issues that might act directly on the volume of the blood vessels. Third, there are issues to be addressed concerning the interstitial compartment relative to the plasma volume.

Addressing the issue of the blood volume, its plasma component could rise if the basis of hyponatraemia was a positive balance of water. On the other hand, and independent of whether hyponatraemia was due to water gain or Na^+ loss, it should cause red blood cell (RBC) swelling. These enlarged RBCs would then occupy more than the usual 2 l of the 5 l of blood thereby increasing the effective circulating volume by close to 240 ml (20% of 2 l = 400 ml) because RBC have close to 60% of their volume as water. Our Professor agreed that while this was likely, his haematocrit had not increased appreciably after his own episode of hyponatraemia due to sweat loss, suggesting that the plasma volume should have increased in parallel with the increased RBC volume.

Focusing on how blood vessels react in order to preserve effective circulating volume, arterial and more importantly, venous vasoconstriction is the expected response in a high adrenergic state. This diminishes the size of the vascular compartment, allowing better filling pressures even though the blood volume was reduced. Nevertheless, our Professor doubted that this mechanism would fully compensate for a loss of close to 1000 mmol of Na^+. Therefore attention was shifted to the interstitial space.

The interstitial fluid could be shifted to the intravascular space if it were either pulled or pushed into the intravascular space. The 'pull' could occur because of hyperalbuminemia due to a lower plasma volume and/or a rise in its Donnan force due to a larger anionic charge on plasma proteins[22] (i.e. a rise in the plasma oncotic pressure). The plasma albumin concentration did not, however, change appreciably in either the Professor or the patient. The other possibility is that the interstitial fluid was 'pushed' into the intravascular space. Our Professor asked the group to think about the effect of a low P_{Na} on the ICF volume. Hyponatraemia causes cell swelling due to a shift of water into cells down an osmotic

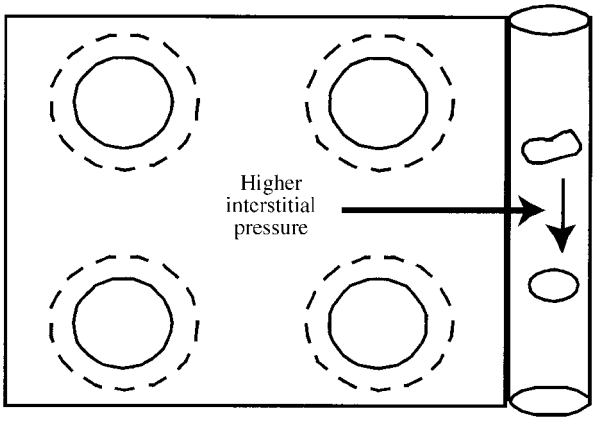

Figure 4. Effect of hyponatraemia on the intravascular volume. The solid circles represent the normal cell volume and the dashed lines the expanded ICF volume during hyponatraemia. The solid rectangle represents the capsule or skull surrounding organs of the body. As the tissue pressure rises, interstitial fluid will enter the vascular compartment as illustrated by the horizontal arrow. Hyponatraemia also causes red blood cells to swell.

difference (the number of osmoles in the ICF compartment is constant). The brain is contained in the skull so that total brain swelling is limited. The first response to hyponatraemia in the brain is to force interstitial fluid and cerebrospinal fluid out of the skull. This makes more space for swollen brain cells without causing herniation syndromes. Similarly, the cells in some other organs of the body are confined by capsules (e.g. liver, kidney) or fascial sheaths around muscles. When these cells swell, the higher interstitial pressure should shift volume from the interstitial space to the intravascular space. Hence, as summarized in Figure 4, hyponatraemia due to a very large deficit of Na^+ could result in a much higher than anticipated intravascular volume. Therefore, one should not discard the hypothesis of a large Na^+ deficit as an initial cause for her hyponatraemia on the basis of it being haemodynamically implausible.

Having focused the entire analysis on Na^+ and water issues, our omniscient clinician then turned his attention to the patient and asked whether there were unique features in our patient that could help explain the rare occurrence of a severe degree of hyponatraemia in this population of young people. More specifically, *'Was there a gender bias in hyponatraemia in this group, he inquired?'*

Question 9: Was there a gender bias in hyponatraemia in this group?

One of the residents had recently reviewed this topic by performing a literature search with the

keywords MDMA, Ecstasy, 3,4-methylenedioxymethamphetamine, hyponatraemia, sodium, toxicology, intoxication, cerebral edema, ADH, antidiuretic hormone, and for the years 1966–2002 (Appendix 1). He confirmed the remarkably high prevalence of acute hyponatraemia in female patients. Of the cases that specifically involved hyponatraemia (P_{Na} range on admission 101–130 mmol/l) and MDMA use, 8 of the 10 subjects were women.[23–29] In contrast, there were many other causes of morbidity and mortality following MDMA ingestion that involved predominantly male patients. Of the 44 cases identified where the complication were not attributable to hyponatraemia, 79% involved men.[20–26]

At this point a question was asked, '*Does the higher incidence of a severe degree of hyponatraemia in women taking MDMA imply a central role for oestrogen or progesterone*?'

Question 10: Does the higher incidence of a severe degree of hyponatraemia in women taking MDMA imply a central role for oestrogen or progesterone?

Physiology principle 7: a smaller muscle mass causes a greater degree of hyponatraemia when a given volume of EFW is retained

The Professor pondered for a moment and then responded. Although he could not think of any obvious link between oestrogen or progesterone and hyponatraemia, he could offer some alternative explanations to account for the gender differences.

The higher incidence of a severe degree of hyponatraemia in women may be related to the lower percentage of muscle-mass that some women may have. Because half of total body water is in skeletal muscle cells, an individual is at high risk for a severe degree of hyponatraemia after a given water load if they have a very small muscle mass. This includes individuals with muscle atrophy from illness or from a nutritional problem (e.g. a patient with anorexia nervosa).

In addition to the above explanation regarding the higher incidence of hyponatraemia in women, young patients also appear to be affected. The age range of patients with hyponatraemia-related ecstasy complications was 15–36 years old (average age 21 years) in the case series analysed by the housestaff. One reason for the young age could be the absence of age-related brain cell atrophy, and thereby a higher proportion of intracellular volume in the brains of younger patients. This means more swollen cell volume within the confined space of the skull if acute hyponatraemia develops. Alternatively, case reports of MDMA and hyponatraemia may be predominantly in young people because it is typically a younger population that takes MDMA and therefore suffers this complication.

Armed with the knowledge that was obtained from the quantitative analysis, our Professor asked, *'How can similar cases be avoided in the future?'*

Question 11: How can similar cases be avoided in the future?

The first and obvious option is to avoid taking MDMA. Prevention of hyponatraemia after MDMA ingestion starts with awareness of the condition. Copious water ingestion should not be regarded as an antidote to unpleasant side-effects and complications of MDMA use. Those serving drinks should be made aware of the complication, and discourage excessive water drinking. Security personnel posted in washrooms and near drinking fountains should play the same role. Furthermore, partygoers should be encouraged to attend in pairs or groups, and to discourage drinking a very large volume of water. Should a member of the group become cognitively impaired for any reason, medical attention should be sought promptly. For example, if an individual at a party becomes obtunded, they should not be left unattended to 'sleep it off' but rather, be brought to medical attention as soon as possible. Administration of hypotonic fluid must be avoided. If the patient has even mild symptoms that can be attributed to hyponatraemia, then urgent therapy, including hypertonic saline, should be considered.[19,20]

Appendix 1: Brief synopsis of the literature

There are at least 10 published case reports describing hyponatraemia after MDMA ingestion. This is unlikely to reflect the true incidence or severity of hyponatraemia. There is a large literature describing the multiple possible complications of MDMA ingestion. Many of these papers, some from the forensic literature, include seizures[30–35] as a possible and common complication of MDMA ingestion. Unfortunately, the P_{Na} was only reported in one of the seven patients in the series described by Milroy *et al.*[35] and was reported to be 'low', and the cause of the patient's convulsions. The same patient is reported to have ingested 14 l of water prior to admission to hospital. Thus, even though hyponatraemia due to MDMA is not frequently reported, it may have been present

in MDMA-related deaths attributed to other clinical pathology. Mild, sub-clinical hyponatraemia related to MDMA ingestion may therefore be far more common than is currently thought. The only patients who have come to medical attention, however, are those who develop severe, symptomatic hyponatraemia.

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