Hyponatremia: Focus on Mortality in the Elderly and Pre-Menopausal Women

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www.RenalNutrition.com
Alphabetical order:

**Abbott:** Grant, Speaker bureau  
**Alexion:** consultation  
**Amgen:** Advisory Board, Speaker bureau  
**DaVita:** grant, medical directorship  
**Fresenius:** Speaker, Consultant  
**Genzyme/Sanofi:** Consultant, proctorship  
**NKF:** Grants, advisory boards  
**NIH:** Study sections, grants  
**Otsuka:** Speaker bureau, consultation  
**Shire:** Speaker bureau, consultation  
**Vifor:** consultation
Hyponatremia
Urgencies and Emergencies

Sodium Intake and IV Fluid
Sodium Intake

Daily Sodium Intake: **100-200 mEq/day**

- 1 meq Na = 23 mg
  - Each g Na = 44 mEq
    - 2 gm Na = 87 mEq
    - 4 gm Na = 174 mEq

- 1 mmol NaCl = 23+35.5=58.5 mg
  - Each gram salt contains 17 mmol NaCl
    - 5 gm salt = 85 mmol NaCl
    - 10 gm salt = 171 mmol NaCl
IV Solutions

Saline Solutions:
- **NS** = 0.9% = 154 mmol/L = 308 mosm/L
- ½ **NS** = 0.45% = 77 mmol/L
- **HTS** = 3% = 512 mmol/L = 1,024 mosm/L
- Super-HTN = 23% = 4000 meq/L (4 meq/cc)

Combination Solutions:
- ½ **NS** + 40 KCl = 117 mmol/L Na⁺/K⁺ (~ ¾ **NS**)
- D5W + 1.5 amps NaBicarb = 72 mmol/L Na
- ½ **NS** + 1.5 amps NaBicarb = 149 mmol/L Na
Low Dietary Sodium Intake: Good or Bad

Lower sodium excretion is associated with higher CVD mortality.

Tertiles of 24-hour urinary sodium excretion are sex-specific based on baseline measures (see Table 2). This analysis includes the outcome cohort (see Figure 1 and Table 1). Regions of y-axis scales drawn in blue indicate range from 0 to 5.

Hyponatremia
Urgencies and Emergencies

<table>
<thead>
<tr>
<th>Sodium Intake and IV Fluid</th>
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<tr>
<td>Osmoregulation vs. Volume Regulation</td>
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</table>
### Comparing Osmo-regulation vs Volume regulation

<table>
<thead>
<tr>
<th>Osmo-regulation</th>
<th>Volume regulation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>What is sensed</strong></td>
<td>osmolality</td>
</tr>
<tr>
<td><strong>Sensors</strong></td>
<td>Osmoreceptors (hypothesalamus)</td>
</tr>
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<tr>
<td><strong>Effectors</strong></td>
<td>1. ADH</td>
</tr>
<tr>
<td></td>
<td>(2. Thirst)</td>
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<td></td>
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<tr>
<td><strong>What is affected</strong></td>
<td>a. Urine Osm</td>
</tr>
<tr>
<td></td>
<td>(b. Water intake)</td>
</tr>
</tbody>
</table>
Which one is better?

**Uosm vs. Urine[Na+K] vs. U-Na**

- Musch & Decaux, QJM 1998:

- 17 pts with chronic SIADH: 2 lit of NS → examined changes in serum Na

- **U-osm** was more reliable than **U [Na+K]** in predicting the magnitude and direction of change in S-Na.

Musch & Decaux, QJM 1998:
Back to Hyponatremia
Sx & Sx of Hyponatremia

- **Rapidity**: Osmolyte adaptation theory (organic solutes)
- **Severity**: Na<120

- Abdominal pain, headache (*alarming in young women!*)
- Lethargy, confusion, nausea, vomiting
- Non-cardiogenic pulmonary edema
- Cerebral edema, seizure, coma, death

*Poor outcome in pre-menopausal women!*

- **But in old patients without acute hypo-Na, there is minimal Sx & Sx**
Prevalence of Hyponatremia in the Hospital and Community

Most Common Electrolyte Disorder in Hospitalized Patients

- [Na+] <136 mEq/L
- [Na+] <126 mEq/L
- [Na+] <116 mEq/L

Data are from the Tan Tock Seng Hospital in Singapore, and are based on 303,577 samples from 120,137 patients available for analysis.

Hospital Acquired Hyponatremia (<135 mEq/L)

The Role of Age

Data are from the Tan Tock Seng Hospital in Singapore, and are based on 303,577 samples from 120,137 patients available for analysis.

Mechanisms of Drug-Induced Hyponatremia

- Antidepressants (TCAs, SSRIs, MAOIs)
- Antipsychotics (phenothiazines, haloperidol)
- Antiepileptics (carbamazepine, valproic acid)
- Antineoplastic agents
- Opiates

↑ Hypothalamic Production of Vasopressin
- Antidepressants (TCAs, SSRIs, MAOIs)
- Antipsychotics (phenothiazines, haloperidol)
- Antiepileptics (carbamazepine, valproic acid)
- Antineoplastic agents
- Opiates

↑ Vasopressin Effect at Renal Tubule Level
- Antidiabetic drugs (chlorpropamide, tolbutamide)
- Antiepileptics (carbamazepine, lamotrigine)
- IV cyclophosphamide
- NSAIDs

Alter Na/H₂O Homeostasis
- Thiazide diuretics/indapamide
- Amiloride
- (Loop diuretics)

MAOIs = monoamine oxidase inhibitors; NSAIDs = nonsteroidal antiinflammatory drugs; SSRIs = selective serotonin reuptake inhibitors; TCAs = tricyclic antidepressants.
Falls are Common Symptoms of Chronic “Asymptomatic” Hyponatremia

Data based on a case-control study in a general Belgium hospital.

Mean Serum [Na⁺]:
- Hyponatremic Patients: 126±5 mEq/L (n=122)
- Controls: 139±2 mEq/L (n=244)

Patients with chronic “asymptomatic” hyponatremia were admitted for falls significantly more frequently than patients with normal [Na⁺] levels

Adjusted OR 67.4 (95% CI 7.5–607.4), P<.001
<table>
<thead>
<tr>
<th>Author and Year</th>
<th>Study design</th>
<th>Mean Serum Na in HyNa group</th>
<th>N</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ayus and Arieff 1999</td>
<td>Prospective study of postmenopausal women with chronic symptomatic HyNa (Na &lt;130 mmol/l).</td>
<td>111± 12</td>
<td>53</td>
<td>19% presented with orthopedic injury.</td>
</tr>
<tr>
<td>McPherson and Dunsmuir 2002</td>
<td>Retrospective study; incidence of moderate HyNa (Na &lt; 130 mmol/l) in patients with hip fractures.</td>
<td>N/A</td>
<td>107</td>
<td>2.8% incidence HyNa at presentation.</td>
</tr>
<tr>
<td>Renneboog et al 2006</td>
<td>Case-control study; prevalence of falls in patients with chronic asymptomatic HyNa (Na &lt; 133 mmol/l) vs. normonatremic controls.</td>
<td>126± 5</td>
<td>244</td>
<td>21.3% incidence of falls in HyNa group vs. 5.3% controls.</td>
</tr>
<tr>
<td>Renneboog et al 2006</td>
<td>Prospective study evaluating gait disorders in patients with chronic asymptomatic HyNa (Na &lt; 132 mmol/l).</td>
<td>128± 3</td>
<td>16</td>
<td>Significant disorders in gait and attention.</td>
</tr>
<tr>
<td>Gankam Kengne et al 2008</td>
<td>Case-control study; Prevelance of HyNa in elderly patients (&gt; 65 years) presenting with and without bone fracture.</td>
<td>131± 3</td>
<td>1,026</td>
<td>13% incidence of HyNa in fracture patients vs. 3.9% in controls.</td>
</tr>
<tr>
<td>Sandhu et al 2009</td>
<td>Case Control study comparing the incidence of mild HyNa (Na &lt; 135 mmol/l) in elderly patients (&gt;65 years) with and without large bone fracture.</td>
<td>131± 2</td>
<td>728</td>
<td>9.1% incidence of HyNa in patients with fractures vs. 4.1% in controls.</td>
</tr>
<tr>
<td>Verbalis et al 2010</td>
<td>Cross sectional cohort study; Evaluation of BMD in patients &gt; 50 yrs with HyNa (Na &lt; 135mmol/l) vs. normonatremic controls in the NHANES III</td>
<td>133 ± 2</td>
<td>N/A</td>
<td>Adjusted OR of osteoporosis in HyNa adults was 2.87 times that among controls.</td>
</tr>
<tr>
<td>Kinsella et al 2010</td>
<td>Cross-sectional cohort study; incidence of HyNa (Na &lt; 135 mmol/l) in women with and without a fracture who underwent previous bone densitometry measurement.</td>
<td>132.2 ± 1.8</td>
<td>1408</td>
<td>8.7% incidence of HyNa in women with fracture vs. 3.2% in those without.</td>
</tr>
<tr>
<td>Hoorn et al 2011</td>
<td>Cross–sectional cohort study; Incidence of falls and fractures in an elderly population with and without HyNa (Na &lt; 136 mmol/l)</td>
<td>133.4 ± 2</td>
<td>5,208</td>
<td>23.8% incidence of falls in HyNa vs. 16.4% is those without. OR of V/ non-V fracture in HyNa 1.39 and 1.78, resp.</td>
</tr>
<tr>
<td>Tolouian R et al. 2011</td>
<td>Case-control study; Patients admitted for hip fracture secondary to fall compared to patients admitted for elective hip or knee replacement</td>
<td>131 ± 2</td>
<td>249</td>
<td>Prevalence of HyNa 16.9% in cases vs. 4.65 in controls (p=0.03). OR=4.80;p=0.04</td>
</tr>
</tbody>
</table>

Chronic Hyponatremia (serum Na <135 mEq/L)

- CNS impairment
  - Unsteady gait
  - Confusion
  - Lethargy

- Osteoporosis
  - ↓ Bone mineral density
  - ↑ Bone resorption
  - Altered bone quality

- Falls
- Fragile bones

Hip fractures

Gait stability assessed in 16 hyponatremic patients ([Na⁺] 124-130 mEq/L)

Patients asked to walk on *pressure mat*. Skew from midline of path measured as length of walk.

**Gait instability significantly increased in hyponatremia**

- 130 mEq/L
- 124 mEq/L

**Gait stability normalized**

- 139 mEq/L
- 135 mEq/L

Correction of hyponatremia

Clinical Symptoms in Severe Hyponatremia

Incidence of Symptoms Observed in Hospitalized Patients With Severe Hyponatremia (serum [Na⁺] <115 mEq/L)

- Altered sensorium: 51.7%
- Seizures: 22.5%
- Nausea/vomiting: 4.8%
- Gait disturbance/frequent falls: 3.6%
- Dysarthric speech: 2.2%
- Comatose: 2.2%

Data from retrospective study of 168 hospitalized patients (89 of whom were symptomatic) with severe hyponatremia (serum [Na⁺] <115 mEq/L) in a US medical center.

Acute Hyponatremia (<36–48 hrs): Severe Cerebral Edema

Normal Brain

Acute/Severe Hyponatremic Brain

Reprinted with permission from Gross P. Kidney Int. 2001;60:2417-2427.
Brain Volume Adaptation With Hyponatremia

Role of Vasopressin (ADH) in the Pathophysiology of Hyponatremia

- Peptide hormone composed of 9 amino acids
- Synthesized within the supraoptic and paraventricular nuclei of the hypothalamus
  - Transported from the hypothalamus via nerve tracts to the neural lobe of the pituitary, where it is released into circulation
- Regulates urinary water excretion

**Vasopressin $V_{1a}$ Receptor Subtype**

### V$_{1a}$ Sites of Action
- Vascular smooth muscle
- Platelets
- Brain
- Hepatocyte
- Uterine muscle
- Adrenal gland

### Physiologic Effects
- Vasoconstriction
- Myocardial hypertrophy
- Platelet aggregation
- Memory, BP and HR regulation, other*
- Glycogenolysis
- Uterine constriction
- Aldosterone and cortisol secretion

*Stress adaptation, social recognition, circadian rhythmicity, temperature regulation.

Vasopressin $V_{1b}$ Receptor Subtype

$V_{1b}$ Sites of Action
- Anterior pituitary
- Brain
- Pancreas

Physiologic Effects
- Release of ACTH/β-endorphins
- Stress adaptation
- Insulin release

ACTH = adrenocorticotropic hormone.
Vasopressin V$_2$ Receptor
Effect of Vasopressin on Renal Water Handling
Which one is **NOT** an emergent case?

A. A 73 y/o Korean woman presenting with 10 days of weakness. She explains her PMD started her 2 wks ago on HCTZ 25 mg qd and told her to drink more fluid to prevent UTI. S-Na is **107 meq/L**.

B. A 20 y/o otherwise healthy Asian College student brought in to ER Saturday AM with confusion, after attending a party Friday evening. S-Na of **123 meq/L**. Pt is obtunded. PE reveals basal crackles. Friends admit that ecstasy was available in the party.

C. A 32 y/o Hispanic woman with s/p appendectomy earlier today has some SoB and mild abd. pain. S-Na is **122 meq/L** post-OP (was 137 meq/L pre-OP this AM).

D. A 26 y/o AA female college student is brought to the urgent care Sunday evening following the LA Marathon. She is mildly confused and breathes slightly heavily. Her S-Na is **121 meq/L**.
Effects of Hyponatremia on the Brain

- Normal brain (normal osmolality)
- Immediate effect of hypotonic state
- Water gain (low osmolality)
- Rapid adaptation
- Loss of sodium, potassium, and chloride (low osmolality)
- Slow adaptation
- Loss of organic osmoles (low osmolality)
- Improper therapy (rapid correction of the hypotonic state)
- Proper therapy (slow correction of the hypotonic state)
- Osmotic demyelination

Adapted with permission from Adrogué HJ et al. N Engl J Med. 2000;342:1581-1589. Copyright ©2000 Massachusetts Medical Society. All rights reserved.
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<td>Normal Saline vs. Hypertonic Saline</td>
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Postoperative Hyponatremic Encephalopathy in Menstruant Women.
Ayus JC, Wheeler JM, Arieff AI.
Menstruant women are about 25 times more likely to die or have permanent brain damage compared with either men or postmenopausal women.

Hyponatremia, Cerebral Edema, and Noncardiogenic Pulmonary Edema in Marathon Runners
Ayus JC, Varon J, Arieff AI
Female marathon runners tend to develop conditions that lead to hyponatremia.
Effect of **Gender** on Brain Damage from Hyponatremic Encephalopathy

Ayus et al, Ann Intern Med 1992

- **All hyponatremic controls (n=674)**
  - Women: 54
  - Men: 46

- **All cases with brain damage (n=34)**
  - Women: 97
  - Men: 3
Effect of **Menstrual Status** on Brain Damage from Hyponatremic Encephalopathy

*Ayus et al, Ann Intern Med 1992*

![Bar chart showing the effect of menstrual status on brain damage from hyponatremic encephalopathy.](chart.png)

- **All female hyponatremic controls (n=367):**
  - Post-menopausal: 89
  - Menstruant: 1

- **All female cases with brain damage (n=33):**
  - Post-menopausal: 24
  - Menstruant: 76
Conclusions

• Women and men are equally likely to develop hyponatremia and hyponatremic encephalopathy after surgery.

• However, when hyponatremic encephalopathy develops, menstruant women are about 25 times more likely to die or have permanent brain damage compared with either men or postmenopausal women.

Ayus et al, Annals, 1992
Postoperative Hyponatremic Encephalopathy in Menstruant Women.
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Ayus JC, Varon J, Arieff AI
Female marathon runners tend to develop conditions that lead to hyponatremia.
Noncardiogenic pulmonary edema with increased intracranial pressure

- 7 healthy marathon runners: The runners collapsed after competing in a marathon and were hospitalized with pulmonary edema.

- INITIAL Sx&Sx: nausea, emesis, abd pain, obtundation
- Serum Na: \(121 \pm 13\) mmol/L
- \(O_2\) sat: <70%.
- EKG and echo: normal
- CXR: Pulmonary edema w/ a normal heart
- CK-MB, troponin, & wedge pressure: not elevated.
- CT of the brain: cerebral edema

Ayus et al, Annals, 2000
Radiographs and scans obtained from a 44-year-old woman who was admitted to the ER with a plasma sodium level of 121 mmol/L and oxygen saturation of 66%. Bibasilar rales and copious pink frothy sputum were noted, and the respiratory rate was 38 breaths/min.
Noncardiogenic pulmonary edema with increased intracranial pressure

- All patients were intubated and mechanically ventilated.

- Rx: HTS (NaCl 514 mmol/L)
  increase S-Na levels by 10 mmol/L in 12 hrs

- Pulmonary and cerebral edema resolved as S-Na ↑

- Poor outcome if not treated:
  hyponatremic encephalopathy → death
  (of cardiopulmonary arrest b/o brainstem herniation).

- **Conclusions:** In healthy marathon runners, noncardiogenic pulmonary edema can be associated with hyponatremic encephalopathy. The condition may be fatal in menstruant females and can be successfully treated with HTS.

# Hyponatremia

Urgencies and Emergencies

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</table>
Case #1 at Harbor-UCLA

- 20 yo female college student, with no significant PMH, was brought to ER after being found down, unresponsive and in respiratory distress. According to friends, she had taken multiple tablets of an unknown drug the night prior and attended a “wild party”. She was found by her friends early in the morning on the floor, unresponsive and foaming at the mouth. Paramedics reported shallow breathing, weak pulse, fixed and dilated pupils and no response to painful stimuli → intubated in ER

- PMH: none
- PSH: none
- NKDA Meds: unknown
- SH: college student at UCX, no known h/o tobacco, alcohol or drug use

- VS: T 94.5(rectal) HR 123  BP 88/49  RR 6 Pulse Ox 80%
- Gen: unresponsive, intubated
- HEENT: pupils fixed and dilated, no corneal or gag reflex, negative doll’s eyes
- Lungs: diffuse crackles bilaterally
- CV: tachycardic, no murmurs/rubs/gallop
- Abd: normoactive bowel sounds, soft, nondistended, no masses
- Rectal: guiaic (+), brown stool in vault
- Ext: no edema, flaccid tone
- Neuro: GCS 1-1-1, no reflexes
In the ER she was emergently intubated upon arrival. She was hypotensive to SBP of 80’s, received 3 liters of NS and was started on dopamine and norepinephrine drips. Labs were drawn at 08:30 AM.

(08:35 AM)

- **Na**: 117
- **K**: 3.4
- **Cl**: 87
- **HCO3**: 15
- **BUN**: 9
- **Cr**: 1.0
- **Gluc**: 287
- **Ca**: 7.8

- **WBC**: 18.3 (82N 15L)
- **Hb**: 13.3
- **Hct**: 38.7
- **Plt**: 310

- **Urinalysis**: 1.015, pH 7.0, ketones 2+, glucose 2+

- **EKG**: Sinus tachycardia, rate 144

- **CXR (07:50)**: severe pulmonary edema

- **Head CT (09:00)**: severe cerebral edema
MDMA-abuser: CT and CXR
Cerebral edema and noncardiogenic pulm. edema

<table>
<thead>
<tr>
<th>Time</th>
<th>Na</th>
<th>Cl</th>
<th>HCO₃</th>
<th>Cr</th>
<th>pH</th>
<th>CO₂</th>
<th>O₂</th>
<th>IVF</th>
<th>Urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:30</td>
<td>117</td>
<td>87</td>
<td>15</td>
<td>1</td>
<td>7.14</td>
<td>37</td>
<td>99</td>
<td>3L NS</td>
<td>2000 ml</td>
</tr>
<tr>
<td>10:00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3% saline (20 ml total)</td>
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<tr>
<td>10:30</td>
<td>121</td>
<td>94</td>
<td>15</td>
<td>0.7</td>
<td>7.29</td>
<td>40</td>
<td>51</td>
<td>1L NS</td>
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<tr>
<td>11:00</td>
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<td></td>
<td></td>
<td>1L NS</td>
<td>180 ml/hr</td>
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<td>12:00</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>3% saline (225 ml total)</td>
<td>200 ml/hr</td>
</tr>
<tr>
<td>13:15</td>
<td>120</td>
<td>91</td>
<td>19</td>
<td>0.9</td>
<td>7.24</td>
<td>29</td>
<td>119</td>
<td>200 ml/hr</td>
<td></td>
</tr>
<tr>
<td>15:30</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7.29</td>
<td>27</td>
<td>75</td>
<td>500 ml NS (drips)</td>
<td>125 ml/hr</td>
</tr>
<tr>
<td>18:00</td>
<td>129</td>
<td>104</td>
<td>17</td>
<td>1.3</td>
<td></td>
<td></td>
<td></td>
<td>300 ml NS (drips)</td>
<td>150 ml/hr</td>
</tr>
</tbody>
</table>

20:15: Code Blue: Pt. with wide-complex tachycardia → PEA → converted to sinus with 500 ml NS and epinephrine → Ten min later: code blue again → brady to 30's

→ PEA→ asystole → expired at 21:43

Fatal hyponatremia in a young woman after ecstasy ingestion
Kamyar Kalantar-Zadeh*, Minhtri K Nguyen, Roger Chang and Ira Kurtz

SUMMARY

Background A 20-year old, otherwise healthy, female college student presented in an unresponsive state with respiratory distress after ingesting ecstasy (3,4-methylenedioxymethamphetamine). She had initial plasma sodium concentration of 117 mmol/l.

Investigations Physical examination, blood chemistry panel, urinary osmolality and electrolytes, arterial blood gas, chest X-ray, and CT scan of the brain.

Diagnosis Hyponatremia associated with noncardiogenic pulmonary edema and cerebral edema.

Management Administration of a total of 6.8 l of isotonic saline and 0.245 l of 3% hypertonic saline with sporadic administration of intravenous furosemide. The patient died approximately 12 h after admission.

KEYWORDS ecstasy, estrogen, hyponatremic encephalopathy, MDMA, noncardiogenic pulmonary edema

This article offers the opportunity to earn one Category 1 credit toward the AMA Physician’s Recognition Award.

THE CASE

In 2002, a 20-year-old, Asian American woman was brought to the emergency room at Harbor-UCLA Medical Center after having taken multiple tablets of ecstasy (3,4-methylenedioxymethamphetamine [MDMA]) and large quantities of water while dancing and drinking excessively during a party the night before. She did not report any symptoms upon returning home after the party. In the morning, however, she was found unresponsive and foaming at the mouth although no seizures were reported. She had rapid and shallow breathing, a weak pulse,
Ecstasy Associated Hyponatremia in Premenopausal Women has a High Risk of Morbidity & Mortality
## Two fatal cases of MDMA toxicity

<table>
<thead>
<tr>
<th>History</th>
<th>Patient 1</th>
<th>Patient 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age and sex</td>
<td>15 y/o female</td>
<td>18 y/o female</td>
</tr>
<tr>
<td>H/o MDMA abuse</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Amount of MDMA</td>
<td>1 ‘ecstasy’*</td>
<td>1 ‘ecstasy’*</td>
</tr>
<tr>
<td>Time of ingestion</td>
<td>Midnight</td>
<td>7:45 PM</td>
</tr>
<tr>
<td>Behavioral pattern</td>
<td>Dancing, talking and drinking water (at least 3 lit)</td>
<td>Smoking cannabis, drinking EtOH + water</td>
</tr>
<tr>
<td>Onset of toxicity</td>
<td>05.00 AM: felt ill, vomited; given more water → convulsed; 08.00 AM: semi-conscious, urinary incontinent; 10.00: confused; SoB</td>
<td>00.15: felt ill; numb legs; drank 6–7 cups of water → vomiting, headache, vision loss, rigidity → respiratory arrest</td>
</tr>
<tr>
<td>Hospital transport</td>
<td>10.30: GCS 3/15; pulse 120; SBP 80; intubated /ventilated, 1.5 Lit IV fluid</td>
<td>00.55: unconscious; intubated/ventilation, IV fluid?</td>
</tr>
<tr>
<td>Hospital presentation</td>
<td>11.30: GCS 3/15; pupils fixed/dilated; absent brain stem reflexes; BP 80/50; T 32.6; 1 L of IV NS</td>
<td>01.30: GCS 3/15; pupils fixed and dilated; papilledema; T 33 °C; BP 108/60</td>
</tr>
<tr>
<td>Investigations</td>
<td>12.00 noon: S-Na 125 mmol/L; calculated serum osmolality 269 mmol/kg; <strong>CXR: pulmonary edema</strong>; CT head: diffuse cerebral edema and cerebellar herniation → IV mannitol, diuretic; 18.00: S-Na 135 mmol/l → declared brain dead on day 2</td>
<td>02.00 AM: S-Na 126 mmol/L; <strong>CXR: pulmonary edema</strong>; CT head: marked cerebral edema, diuretic + IV NS; 09.00 AM: S-Na 145 mmol/L; 2 L negative fluid balance → declared brain dead on day 3</td>
</tr>
<tr>
<td>Post-mortem findings</td>
<td><strong>Brain swollen</strong> with evidence of herniation; haemorrhage in the vicinity of the pituitary</td>
<td>Brain diffusely softened and swollen, vessels distended, severe hypoxic brain damage</td>
</tr>
<tr>
<td>Ante-mortem blood toxicology</td>
<td>MDMA 0.05 mg/l</td>
<td>MDMA 0.209 mg/l; MDA 0.029 mg/l Ethanol 0.8 g/l</td>
</tr>
</tbody>
</table>

From: Hartung et al. Hyponatraemic states following 3,4-methylenedioxymethamphetamine (MDMA, ‘ecstasy’) ingestion. *QJM* 2002; 95(7):431-437
Ecstasy → Hyponatremia

- **One single Mechanism?**
- **Most likely combination of several mechanisms:**
  - Inducing ↑ADH
  - Increasing urine osm (similar to thiazide)?
  - Exercise → sweating → ↑ water intake
  - Nausea & vomiting → ↑ water intake
  - Water accumulation in GI → ↑ water absorption
  - In the hospital → ↑ IV fluid (NS)
High incidence of mild hyponatraemia in females using Ecstasy at a rave party

FIGURE 1: Plasma sodium of all participants. The plasma sodium 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 nonusers (141 ± 2.0 mmol/L, range 137–145 mmol/L, P < 0.001)
# Hyponatremia Urgencies and Emergencies

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</table>
Case #2: Marathon Runner

- **38-year-old**, otherwise healthy Caucasian **female** presented to the ER at 7:00 PM on Sat with **acute respiratory distress**, nausea, vomiting, lose stools and **headache** after a 10-hour run of the annual San Francisco Marathon (~ 40 miles).
- She had drunk ~ 25 bottles of water (8.5 onz each).
- Upon returning home, she experienced headache and mild **abdominal pain** and became somewhat **confused**.
- In the ER: **RR 35**; **HR 120**, **BP 150/90**, **O2 sat 85%** on 4-6 L O2.
  + **Bilateral basal crackles**
  + nonspecific abdominal tenderness periumbilically
  + non-focal neurological examination.
- **Lab**: serum **sodium 121 mEq/L**, Urine **specific gravity 1.020**. ABG: **PH 7.73**, **pCO2 9 mmHg**, **pO2 57** mmHg.
- A spot urine sample one hr after the above tests showed a urine osmolality of 245 mosm/kg and urine sodium 31 mEq/L.
- **Nephrology consult recommended IV HTS**, which was questioned by ER physician and intensivist on call.
Marathon Runner: CXR
non-cardiogenic pulmonary edema

Case #3: Post-OP Young Female

- 24-year-old Caucasian female, admitted with the working diagnosis of acute appendicitis and underwent appendectomy in the evening.
- Pre-OP S-Na 141 mEq/L. Blood sugar 55 mg/dL on admission → started on IV D5W, which was also administered overnight post-OP to avoid hypoglycemia.
- POD#1 AM: c/o headache and SoB. BP 106/55, HR 94, RR 30, O2 sat 88% on RA. PE: mild to moderate respiratory distress, + rales on both lungs. +mildly to moderately obtunded.
- Post-OP AM S-Na 119 mEq/L, S-osm 249 mosm/kg, U-osm 210 mosm/kg. CXR: Pulmonary vascular congestion and edema.
- Surgery: d/c’ed IVF + gave IV Lasix 40 mg → 2.5 liters of U/O over 4 hrs
- Nephrology consult in the afternoon: S-Na 130 mEq/L → expressed major concerns re “excessively rapid rate” of correction → recommended D5W or ½ NS to be reinstituted.
- Meanwhile, pt’s respiratory and neurological Sx improved. Surgery disregarded concerns/recommendations of nephrology.
- Pt was discharged home the following day with a final S-Na 136 mEq/L and without any respiratory or neurological issues.
PROJECTED MORBIDITY FROM POSTOPERATIVE HYPONATREMIA IN THE USA

- Total surgeries in the USA: 25 million
- Postoperative hyponatremia: 250,000
- Hyponatremic encephalopathy: 25,000
- Hyponatremic brain damage or death: 10,000

<table>
<thead>
<tr>
<th></th>
<th><strong>Ecstasy user</strong></th>
<th><strong>Marathon runner</strong></th>
<th><strong>Post-surgical pt</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age and gender</strong></td>
<td>20 years old female</td>
<td>38 years old female</td>
<td>24 years old female</td>
</tr>
<tr>
<td><strong>Preceding events</strong></td>
<td>Ecstasy, dancing, excessive water</td>
<td>40 mile marathon + 25 bottles of water</td>
<td>D5W pre- &amp; post-OP to avoid hypoglycemia</td>
</tr>
<tr>
<td><strong>Initial serum sodium</strong></td>
<td>117 mEq/L</td>
<td>121 mEq/L</td>
<td>119 mEq/L</td>
</tr>
<tr>
<td><strong>Serum osmolality</strong></td>
<td>245 mosm/kg</td>
<td>253 mosm/kg</td>
<td>249 mosm/kg</td>
</tr>
<tr>
<td><strong>Urine osmolality (Uosm) and/or specific gravity (SG)</strong></td>
<td>SG: 1.015</td>
<td>Uosm: 245 mosm/kg</td>
<td>Uosm: 210 mosm/kg</td>
</tr>
<tr>
<td><strong>Initial symptoms</strong></td>
<td>Found unresponsive the morning after</td>
<td>Confusion, headache, abdominal pain, SoB</td>
<td>Headache and shortness of breath</td>
</tr>
<tr>
<td><strong>Symptoms upon presentation</strong></td>
<td>Coma</td>
<td>Tachycardia, tachypnea respiratory distress</td>
<td>Respiratory distress and obtundation</td>
</tr>
<tr>
<td><strong>Respiratory distress</strong></td>
<td>Severe respiratory distress; intubated</td>
<td>Mod. respiratory distress hypoxemia</td>
<td>Mild to mod. resp distress &amp; rales on both lung</td>
</tr>
<tr>
<td><strong>Oxygen saturation</strong></td>
<td>80% on NR mask</td>
<td>82% to 88% on 4-6 N/C</td>
<td>88% to 92% on room air</td>
</tr>
<tr>
<td><strong>CT-scan of the head</strong></td>
<td>Pulmonary edema</td>
<td>Pulmonary edema</td>
<td>Pulmonary edema</td>
</tr>
<tr>
<td><strong>Initial IV fluid/medications administered</strong></td>
<td>Essentially NS (4 lit NS)</td>
<td>HTS + NS + furosemide</td>
<td>IV fluids d/c’ed, and IV Lasix administered</td>
</tr>
<tr>
<td><strong>HTS recommendation questioned by other physicians</strong></td>
<td>ER, med. and neph teams expressed concerns re HTS</td>
<td>Nephrologist presented recent annals paper to ER doc re HTS</td>
<td>Neither nephrology team nor other physicians recommended HTS</td>
</tr>
<tr>
<td><strong>Repeat/final serum sodium</strong></td>
<td>129 mEq/L after 10 hrs</td>
<td>125 mEq/L after 2.5 hrs</td>
<td>136 mEq/L after 24 hrs</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>Death</td>
<td>Improved with no sequelae</td>
<td>Improved with no sequelae</td>
</tr>
</tbody>
</table>

Kalantar-Zadeh et al, 2006 [1]
Pre-menopausal Women & Hyponatremia

Ayus-Arieff Syndrome

• Even borderline ACUTE hypo-Na is a serious condition.
• Most often encountered scenarios:
  – Post surgery in the hospital
  – Marathon runners, jogging, hiking
  – Ecstasy abuse with dancing and drinking

• Abdominal pain and mild headache along with mild change in MS are alarming signs and symptoms!

• Nausea/vomiting with subsequent water intake or IV fluid administration deteriorates the condition.

• Non-cardiogenic pulmonary edema and brain edema can develop rapidly leading to death.

• Rx: Hypertonic saline despite pulm/cereb. edema!
Why are women at Risk?

Ecstasy-associated hyponatremia: why are women at risk?

Michael L. Moritz\(^1\), Kamyar Kalantar-Zadeh\(^2,3\) and Juan Carlos Ayus\(^4,5\)

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\(^2\)Harold Simmons Center for Kidney Disease Research and Epidemiology, Division of Nephrology and Hypertension, University of California Irvine Medical Center, Orange, CA, USA,
\(^3\)Department of Epidemiology, UCLA Fielding School of Public Health, Los Angeles, CA, USA,
\(^4\)Renal Consultants of Houston, Houston, TX, USA and
\(^5\)Hospital Italiano, Buenos Aires, Argentina

- Moritz, Kalantar-Zadeh, Ayus, Ecstasy Associated Hyponatremia: Why are women at Risk? NDT 2013
Ayus-Arieff Syndrome: Why Young Women?

- **ESTROGENIC hormones**: 2 possible mechanisms:
  - (1) inhibition cerebral Na-K-ATPase activity
    → impairs the ability of brain cells to extrude Na+ in initial defense of cell volume
  - (2) increased vasoconstriction of cerebral blood vessels by vasopressin,
    → decrease of brain perfusion

- **LESS MUSCLE MASS** in young women:
  - half of total body water is in skeletal muscle cells!
  - low muscle mass → high risk for severe hyponatremia when a given volume of electrolyte-free water is retained.
  - Individuals with muscle atrophy (anorexia nervosa) are also at risk.

- **BRAIN ADAPTATION** differences:
  - women may be less able to adapt to cerebral edema than men

- **AGING → BRAIN CELL ATROPHY**
  - Young patients are affected more often, possibly due to the absence of age-related brain cell atrophy
    → higher proportion of intracellular brain volume.
    → greater increase in cell volume within the confined space of the skull if acute hyponatremia develops

Ayus-Arieff Syndrome: **Women at Risk?**

Table 1. Relationship between female gender and risk of developing hyponatremia or hyponatremic encephalopathy

<table>
<thead>
<tr>
<th>Setting</th>
<th>Hyponatremia</th>
<th>Hyponatremic encephalopathy in females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-operative</td>
<td>—</td>
<td>++</td>
</tr>
<tr>
<td>Ecstasy</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Exercise</td>
<td>+/-</td>
<td>++</td>
</tr>
<tr>
<td>Desmopressin</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>SSRI</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Thiazide</td>
<td>—</td>
<td>++</td>
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</tbody>
</table>

Moritz, Kalantar-Zadeh, Ayus, Ecstasy Associated Hyponatremia: Why are women at Risk? NDT 2013
Effects of Hypoxemia on Hyponatremic Encephalopathy

Non-Cardiogenic Pulmonary Edema

Moritz, Kalantar-Zadeh, Ayus, Ecstasy Associated Hyponatremia: Why are women at Risk? *Nephrol Dial Transplant* 2013
Effects of Hypoxemia on Hyponatremic Encephalopathy

Non-Cardiogenic Pulmonary Edema

Brain Edema

Vasogenic Edema

Cytotoxic Edema

Tumors – Infarcts
Hemorrhage – Meningitis

Ischemia – Hypotonicity

Glutamate Release from Brain cells

Glutamate Toxicity

NS as Hypontremia Rx?

- Can NS worsen hypo-Na? Yes! Esp if U-osm>>300

- A 60 y/o woman has a serum Na 112 meq/L and U-osm of 600 mosm/kg. 2 lit of NS is administered. Serum Na decreases to 109 meq/L. What happened?

  - 1 Lit NS = 150 meq Na = 300 mosm
  - 2 Lit Ns = 300 meq Na = 600 mosm
  - One lit of urine excretes the whole administered solute
  - One lit of pure water is retained

➤ Give FUROSEMIDE along with NS, in order to diminish the concentrating ability of renal tubules.
Which one is better?

Uosm vs. Urine[Na+K] vs. U-Na

• Musch & Decaux, QJM 1998:
  • 17 pts with chronic SIADH:
    2 lit of NS → examined changes in serum Na
  • U-osm was more reliable than U[Na+K] in predicting the magnitude and direction of change in S-Na.

2 lit of NS to 17 pts with SIADH → changes in S-Na

Musch & Decaux, QJM 1998
TREATMENT of Hyponatremia
*If not developed acutely, is NOT an emergency!*

1. **Water Intake Restriction**
   - Edematous sates, SIADH, primary polydipsia, advanced CKD

2. **Salt Administration**
   - (saline only if U-osm<300, salt tablets)
   - Volume depletion, s/p diuretics, adrenal insufficiency

*Target Correction (if not developed acutely):*
- ≤10 meq/L/day
- ≤ 0.5 meq/L/hr

Oral vaptans can only be initiated & re-initiated in the hospital ➔ Advise drinking water if thirsty
Hyponatremia: Strategies for Correction

1. Add to the numerator

\[ \text{Serum } [\text{Na}^+] \sim \frac{\text{Na}^+_E + \text{K}^+_E}{\text{Body water}} \]

2. Subtract from the denominator

Acknowledge Communication by R. H. Sterns.
NS may worsen Hyponatremia

Kovesdy et al, CIRCULATION 2012

Association of sodium with mortality in a national cohort n=655,493 US veterans with CKD (n=95,961 [15%] of them with CHF).
No Worsening or Improvement in Outcomes
EVEREST Trial, All Patients

All-Cause Mortality
HR 0.98; 95%CI (0.87–1.11)
Meets criteria for non-inferiority

CV Mortality or HF Hospitalization
HR 1.04; 95%CI (0.95–1.14)

<table>
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<tr>
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</table>
Risk of Osmotic Demyelination: Central Pontine Myelinolysis

Due to osmotic shrinkage of brain cells.

In Rx of chronic or slowly progressive hypo-Na
if Na rise >20 meq/24hrs

MS changes, dysphagia, Babinski, paraparesis, coma

Dx: MRI (may not be + for up to 4 wks!)

In uremic/CKD/ESRD pts with hypo-Na: CPM is rare!
> b/o concurrent removal of urea during dialysis?
> azotemia expedites intracellular osmolyte shift?
A 30-y/o alcoholic woman presented with confusion and disorientation after a grand mal seizure. The pt's serum Na on admission was 99 mmol/L. Treatment was initiated with a slow infusion of NS, resulting in serum Na values of:

- 102 mmol/L 4 hours after admission,
- 104 mmol/L at 8 hours,
- 115 mmol/L at 12 hours,
- 118 mmol/L at 18 hours,
- 125 mmol/L at 24 hours.

The pt initially had dysarthria, with slurred speech, and a slow finger-to-nose test on cerebellar examination, although there was no Babinski reflex.

During days 2 to 6 with a normal serum Na concentration, her condition gradually improved, although she interacted slowly with staff members and family, and had difficulty following commands.

MRI of the brain (3rd day) was negative for CPM.

On the 7th day she became unresponsive to commands and painful stimuli and had a Babinski reflex.
Second MRI (7th day) demonstrates **central pontine myelinolysis** as a region of prominent low signal intensity on a sagittal T1-weighted image and high signal intensity on an axial T2-weighted image. The signal intensity on the periphery of the pons is normal on both images, and there is relative preservation of the corticospinal tracts (Panel B, arrowheads).

The patient remained in an unresponsive state for 7 weeks, but her sensorium gradually improved until she was fully responsive, alert, and oriented.
# Hyponatremia

## Urgencies and Emergencies

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<th>Description</th>
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CONCLUSIONS: Hyponatremia

• Hyponatremia is the most common electrolyte disarray.

• The treatment urgency depends on the rate of development and patient’s age and gender.

• Pre-menopausal women are at high risk of morbidity and mortality even with mild hypo-Na.

• Non-cardiogenic pulmonary edema and cerebral edema are fatal conditions in these patients.

• Elderly individuals are at high risk of “over-treatment” for otherwise clinically stable hyponatremia.
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