Hyponatremia

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The Kidney in the Olympic News

A Chinese swimmer has tested positive for “diuretic” doping at the Olympics. Very commonly used to dilute the urine and mask the use of PEDs. 8% of all WADA positive tests. I personally would use a loop diuretic or vaspressin antagonist. HCTZ could be important in our lecture today!!!
Hyponatremia in the News

Athlete dies after IM Frankfurt

A 30-year-old British age group athlete died in a Frankfurt hospital several days after he collapsed at the finish of the 2015 Ironman European Championships on a very hot day, report various newspapers in Germany.

Fort Benning soldier, 21, dies following medical complication

FORT BENNING, GA (WTVM) - A Fort Benning Soldier died Wednesday at the Midtown Medical Center, where he was being treated for hyponatremia.

Second Lt. Michael R. Parros, 21, of Walnut Creek, Calif., was in his first day of U.S. Army Ranger School on July 25, when he fell ill and was transported for medical treatment.

"This is a tragic loss," said Lt. Col. Matthew Weber, Commander of the 2nd Battalion, 11th Infantry Regiment. "While 2nd Lt. Parros was only with us for a short time, he showed so much potential and was the epitome of the kind of Soldier you want to serve with. We are truly saddened to lose a member of our Army family."

Parros, who reported to Fort Benning for training on June 27, graduated from the U.S. Army Military Academy in May, as an...

“Swelling of the brain is the cause of death and it was likely caused by insufficient salt intake while racing in unusually hot conditions.”

“The athlete drank mostly water during the race and did not take in enough minerals. “

Military incidents of hyponatremia increased dramatically, with 125 cases between 1989 and 1996, including at least six deaths, according to a 2006 University of Cape Town study

New fluid guidelines in the military were published July 18, 2016
Football player's death leads to discussion about hyponatremia

Walker Wilbanks died after football game

Drinking too much water and sports drinks may lead to death

The recent deaths of two high school football players illustrate the dangers of drinking too much water and sports drinks, according to Loyola University Medical Center sports medicine physician Dr. James Winger.

Over-hydration by athletes is called exercise-associated hyponatremia. It occurs when athletes drink even when they are not thirsty. Drinking too much during exercise can overwhelm the body's ability to remove water. The sodium content of blood is diluted to abnormally low levels. Cells absorb excess water, which can cause swelling -- most dangerously in the brain.

Georgia football player Zyrees Oliver reportedly drank 2 gallons of water and 2 gallons of a sports drink. He collapsed at home after football practice, and died later at a hospital.

A previous study co-authored by Winger found that almost half of recreational runners in the Chicago area may be drinking too much fluid during races.

And in recent years, there have been more than a dozen documented and suspected runners' deaths from hyponatremia.
Wii radio contest fatality results in $16.5 million verdict

Mother-of-three's surviving family wins lawsuit against organizers of "Hold Your Wee for a Wii" promotion.

by Brendan Sinclair on October 30, 2009

The family of a California woman who died trying to win a Wii in a radio contest has been awarded $16.5 million in its suit against the station, according to the Associated Press.

When the Wii debuted in November of 2006, demand for the system far outstripped supplies, leading some people to go to extremes to get their hands on one. One such person, Jennifer Strange of Rancho Cordova, California, entered a January 2007 "Hold Your Wee for a Wii" radio contest with the system as a grand prize.

After drinking an estimated two gallons of water without urinating or vomiting, the 28-year-old mother of three told a colleague that she felt sick and had a "really bad" headache. She was later found dead in her suburban home, apparently from water intoxication. Drinking excess amounts of water causes the problem of too little sodium in the body (hyponatremia) and can cause swelling of the brain, vomiting, headaches, seizures, coma, and, in extreme cases, death.
The hiker who died from drinking TOO MUCH water: Excess fluid and lack of food caused her brain to fatally swell

- Unidentified 47-year-old woman was hiking through the Grand Canyon
- Fainted at the end of the hike and then collapsed again en route to hospital
- Too much water and exercise caused sodium levels in her blood to fall
- Water rushed into her cells, causing her brain to swell and killing her

By MADLEN DAVIES FOR MAILONLINE
PUBLISHED: 10:49 EST, 5 October 2015 | UPDATED: 13:21 EST, 5 October 2015

Doctors said she had suffered a severe brain swelling from ‘water intoxication’ which led to pressure in the skull, the brain tissues moving, and ultimately ‘brain death’.

According to the woman’s husband, she ‘drank a large amount of water and ate very little’ on the hike.

The large amount of water she consumed, along with the strenuous hiking, meant vital salt and mineral levels in the body were diluted.
Montague family awarded $34M in malpractice suit after mother suffers brain damage

Manganiello, then 42, of Montague, went to a Port Jervis, N.Y., hospital for treatment of a low sodium level. She left with a brain injury that took away much of her physical movement and her speech.

The onetime calculus teacher

The jury accepted the Manganiellos' contention the hospital — and specifically, the physician, Moinuddin Ahmed, and a nurse, Rose Aumick — created Diane Manganiello's condition by giving her too much sodium too quickly.

Patients suffering from hyponatremia — or a low sodium level — should have their sodium raised slowly, no more than 10 to 12 units over 24 hours, Winters said. However, Diane Manganiello’s level was raised 27 units in 14 hours, causing irreversible brain damage, said Winters, who has an office in Parsippany.
Strange but True: Drinking Too Much Water Can Kill

In a hydration-obsessed culture, people can and do drink themselves to death.
62% of all physicians do not know the correct rate of correction of hyponatremia.

15% of all physicians especially internists do not know the correct use of vaptans in hyponatremia.
Lecture Objectives

- Establish the definition of Hyponatremia
- Review the clinical consequences of hyponatremia
- Discuss the physiology of ADH production and action
- Outline the causes of hyponatremia
- Describe the treatment options to acute and chronic hyponatremia
Case Presentation

- A 25 year old woman with laparoscopic appendectomy 2 days ago
- Moderate postop ileus and generalized abdominal pain
- Now not feeling well with a headache and nausea

Medication
- Morphine prn
- D5 0.45 NS 125 cc/min – total of 6 liters in 2 days

<table>
<thead>
<tr>
<th></th>
<th>Na</th>
<th>K</th>
<th>Cl</th>
<th>HCO3</th>
<th>BUN</th>
<th>Cr</th>
<th>Glucose</th>
<th>Osm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current</td>
<td>125</td>
<td>3.5</td>
<td>90</td>
<td>20</td>
<td>6</td>
<td>0.5</td>
<td>90</td>
<td>257</td>
</tr>
<tr>
<td>Pre op</td>
<td>140</td>
<td>4.1</td>
<td>95</td>
<td>25</td>
<td>9</td>
<td>0.7</td>
<td>95</td>
<td>288</td>
</tr>
</tbody>
</table>
How would you describe her neurologic condition?

A. Osmotic Demyelinating Syndrome with cerebral edema
B. Hyponatremic Encephalopathy with cerebral edema
C. Osmotic Demyelinating Syndrome with an acute decrease in cerebral volume
D. Hyponatremic Encephalopathy with an acute decrease in cerebral volume
E. Osmotic Demyelinating Syndrome with no change in brain volume
F. Hyponatremic Encephalopathy with no change in brain volume
G. Subdural hematoma secondary to Hyponatremia
H. Acute CVA secondary to Hyponatremia
How much water can you (normal person) drink before you become hyponatremic?

A. 3 L
B. 6 L
C. 10 L
D. 18 L
E. 25 L
F. 30 L
G. With normal renal function the sky is the limit! Drink away! Last month I bought the unlimited drink package on a cruise ship and I got my money’s worth and my brain is fine (I think!)
What is your target sodium level and how quickly should you correct symptomatic patients with hyponatremia to avoid seizures?

A. Correct up to a Na of 135 meq/L within 24 hours
B. Correct up to a Na of 130 meq/L within 24 hours
C. Correct no more than 15 meq/L within 24 hours
D. Correct no more than 12 meq/L within 24 hours
E. Correct no more than 10 meq/L within 24 hours
F. Correct no more than 6 meq/L within 24 hours
**Definition**

- **Hyponatremia** is defined as
  - Plasma sodium < 135 meq/liter

- **Mild** Hyponatremia is defined as
  - Plasma sodium 130 - 134 meq/liter

- **Moderate** Hyponatremia is defined as
  - Plasma sodium 121 – 129 meq/liter

- **Severe** hyponatremia is defined as
  - Plasma sodium < 120 meq/liter

*Hypernatremia* is defined as

- Plasma sodium > 145 meq/liter
Hyponatremia

• Most common electrolyte abnormality in hospitalized patients (30%)
  - 5% with Na < 125 meq/L

Hyponatremia can be a normal finding
In Pregnancy hyponatremia is a natural and expected result
Normal Na in pregnancy- 130 meq/L
A normal Na in pregnancy is abnormal !!! Nd indicates loss of water i.e. volume depletion or pre-eclampsia (third spacing of fluid)
Hyponatremia

Direct CNS Neurotoxicity

Marker for Increased Mortality

Cerebral Edema

CHF Cirrhosis Cancer
Hospital Mortality and Hyponatremia

Mortality increases as serum Na < 135

Restrictive cubic spline transformation plot with 95% confidence intervals is shown. Adapted with permission from Gheorghiade M, et al. Eur Heart J. 2007;28(8):980-988.
Hyponatremia is associated with a Graded Increase in Short and Long Term All Cause Mortality

Clinical Consequences of Hyponatremia

Cerebral edema
Herniation
Which Cells Swell in the Brain?

- Neurons
- Glial Cells
  - Ependymal
  - Astrocytes (Aquaporin4)
  - Oligodendrocytes
  - Microglial

Red 'X': Neurons do not swell.
Green '✓': Glial Cells swell.
Brain Herniation in Hyponatremic Encephalopathy (HE)

Normal Cerebellar Herniation
It is suggested that one of the most common unsuspected contributing factors causing falls in the elderly is hyponatremia!
Hyponatremia and Fractures

Complications of Hyponatremia

**Acute**
- Dizziness/ataxia
- Confusion
- Disorientation
- Seizures
- Increased Mortality

**Chronic**
- Dizziness/ataxia
- Confusion
- Fractures
- Osteoporosis
- Increased mortality

Total cost 1.6 – 3.6 billion dollars / year
Hyponatremia and CNS Disease

Consequence of the actual serum Na concentration

Hyponatremic Encephalopathy (HE)

\[ \text{Consequence of the treatment of the serum Na concentration} \]

Osmotic Demyelinating Syndrome (ODS)
The majority of cases of Hyponatremia are due to excessive water retention with or without a lesser component of Na (solute) loss.
To Understand Hyponatremia We Must Understand Water Balance

Arginine Vasopressin (ADH)
**Total Body Water**

*Total Body Water (TBW)*

- **Extracellular (1/3)**
  - Plasma
  - Interstitial

- **Intracellular (2/3)**

- TBW = 60% of total body weight for a man
- TBW = 50% of total body weight for a woman

- 3.5 L (1/12)
- 11.5 L (1/4)
- 14 L
- 28 L (2/3)

Osmolality of Plasma = Osmolality of Interstitial Fluid = Osmolality of Intracellular Fluid
Changes in the Na concentration in the plasma are related predominately to changes in total body water resulting in a dilution of the number of osmoles.
Plasma Na concentration

Water Balance (Intake / Output)

Anti-Diuretic Hormone (ADH / Vasopressin)
Plasma Na concentration

Na Balance (Intake/Output)

Extracellular Fluid Balance
Edema (pulmonary / lower extremity)
Physiologic ADH Stimuli

Volume

Indirect Stimulation

Baroreceptor Stimulation of Angiotensin II And Sympathetic Nervous System

Tonicity

Direct Stimulation

Paraventricular nucleus

Supraoptic nucleus
Sensors of ECF Volume

- **Cardiopulmonary**
  - Atria (distension)
  - Ventricles (distension)
- **Arterial**
  - Aortic Arch (pressure)
  - Carotid sinus (pressure)
- **Renal**
  - Afferent arteriole (pressure)
  - Macula Densa (NaCl delivery)

Signals via cranial nerves IX and X to the nucleus tractus solitarius (NTS) in the brain stem

Hypothalamus
Volume results in an exponential increase in ADH secretion.

Osmolality results in a linear increase in ADH secretion.

Stimuli for Vasopressin Secretion
Key Principle

The Body Protects Volume over Tonicity When the Change in Volume is $> 10\%$
ADH Mechanism

Cortical and Medullary Collecting Ducts

Adenyl cyclase → Cyclic AMP → Aquaporin (Water channels AQP2)

Aquaporin (Water channels AQP3, AQP4) – Always present
Hyponatremia
Rule #1

Almost all cases of hyponatremia are associated with inappropriate ADH stimulation AND limited dietary intake that limits the degree of water diuresis.
### Your Diet Affects How much Water You can Drink

<table>
<thead>
<tr>
<th>ADH</th>
<th>Urine Specific Gravity</th>
<th>Maximum Fluid intake Before Hyponatremia (Normal Diet 900 mosm)</th>
<th>Maximum Fluid intake Before Hyponatremia (Reduced Diet 450 mosm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>1.003</td>
<td>18 L</td>
<td>9 L</td>
</tr>
<tr>
<td>+</td>
<td>1.010</td>
<td>3 L</td>
<td>1.5 L</td>
</tr>
<tr>
<td>++</td>
<td>1.015</td>
<td>2 L</td>
<td>1 L</td>
</tr>
<tr>
<td>+++</td>
<td>1.020</td>
<td>1.5 L</td>
<td>0.75 L</td>
</tr>
</tbody>
</table>

Dietary oral intake is just as important as ADH regulation in controlling water balance. Simply feeding a patient can markedly improve hyponatremia.
How much Water can you drink before you will get Hyponatremia?

With a normal diet of 900 mosm / day

So how much water intake is too much?

18 liters
Hyponatremia in Heart and Kidney Failure: It is All about the Underfilled Circulation and ADH

Low Cardiac Output – Decreased Effective Circulation Volume

↑ ADH

Serum Na Concentration

Portal HTN - Ascites
Decreased Effective Circulation Volume

↑ ADH

Serum Na Concentration
Nonosmotic States of Arginine Vasopressin Release

Hemodynamic stimuli
- Volume depletion
- Hypotension
- Congestive heart failure
- Cirrhosis
- Nephrotic syndrome
- Adrenal insufficiency

Nonhemodynamic stimuli
- Pain and stress
- Nausea and vomiting
- Hypoxemia and hypercapnia
- Hypoglycemia
- Medications
- Perioperative state
- Inflammation
- Cancer
- Pulmonary disease
- CNS disease
Drug Induced SIADH

- HCTZ
- Narcotics
- MDMA (Ecstasy)
- NSAIDs
- SSRIs
- Vincristine
- Cyclophosphamide
Hospital Acquired Hyponatremia

Osmotic or Non Osmotic Release of ADH + Hypotonic IV Fluid = Hyponatremia
Iatrogenic Hyponatremia in the Hospital

• Avoid the use of ..... 
  – 0.45 NS 
  – D₅W

Conclusion
• The routine use of hypotonic solutions for hospitalized patients is not justified
• Most inpatients have non osmotic release of ADH and are at risk of hyponatremia
• Isotonic IV fluids should be the standard of care
The use of an isotonic IV solution is effective to reduce the risk of hyponatremia.

Exercise Associated Hyponatremia (EAH)

- Combination of solute loss (sweating) and hypotonic fluid intake (sports drinks)
- Common in Endurance Sports activities
  - Marathon
  - Triathlon
  - Hiking
  - Cycling
  - Football training camps
  - Military training camp
  - Police training

\[ ADH \quad \uparrow \quad \text{~ 80 mosm/L} \quad + \quad \text{~ 0 mosm/L} \]
Hyponatremia: YES or NO

**Thiazides**
Distal tubule
Na-Cl channel

**Loop Diuretics**
TALH
Na-K - 2Cl channel
Diuretics and Hyponatremia

• **Facts**
  – Diuretics DO NOT cause hyponatremia because they lead to increased urinary sodium losses (Natriuresis)
    • They can not cause more Na loss than water !!!
  – Only Thiazides (weaker diuretic) cause Hyponatremia while Loop Diuretics (more potent) DO NOT
• Thiazides do not interfere with the urine concentrating mechanism
• Loop diuretics inhibit the development of a medullary hyperosmolar state by preventing the movement of NaCl into the interstitium at the TALH
Non Osmotic / Non Volumetric Causes of SIADH

- Malignancies
  - Small Cell carcinoma (oat cell) of the lung
    - 10-15% incidence
    - m-RNA for AVP
  - Head and Neck squamous cell carcinomas
    - 7% incidence
  - Non-small cell carcinoma of the lung
Hyponatremia

Rule #2

Always check serum osmolality
If < 270 mosm/L : you have
true **Hypotonic Hyponatremia**

**DANGER**

Cerebral edema
Hyponatremia

- Only clinically dangerous if it is associated with
  - Hypotonicity
    - Serum Osmolality / Tonicity < 270 mosm/L

- Do not get tricked by hyponatremia associated with a normal or high serum osmolality / tonicity
  - This condition is called Pseudohyponatremia
  - These patients will NOT develop cerebral edema
Pseudohyponatremia

Hyperglycemia or Mannitol

Hypertonicity pulls Na free water out of the intracellular compartment leading to dilutional hyponatremia

No brain swelling will occur because the patient is not hypotonic (< 270 mosm/L) !!!
They are Hypertonic (>300 mosm/L)


**Pseudo-Hyonatremia**

- A machine analyzer error produced by excess
  - Protein (Multiple Myeloma)
  - Lipids (Hypertriglyceridemia- > 1000 mg/L)

- Etiology
  - Displacement of the plasma by an increase in the semi-solid phase

- Complete Artifact! No actual hypotonicity – No treatment needed
PREVENTION WORKS!

TIME TO ADAPT
Hyponatremia: Cellular Response

Regulatory Volume Decrease

Major Pathways
Immediate: K efflux

After 48 hours:
Extrusion of organic Osmolytes (solutes) such as inositol

Full adaptation requires a minimum of 48 hours

= organic osmoles

= water molecule
Organic Osmolytes

Maintenance of Intracellular Fluid Volume

Myo-inositol, Glutamate, Taurine
Risk Factors for Hyponatremic Encephalopathy

- Rate of onset < 48 hrs
  - Decreased time for brain adaptation
- Age < 16 yrs
  - Increased ration of brain mass to intracranial volume (space)
- Pre-Menopausal
  - Estrogen limits brain adaptation
    - Increases ADH
    - Vasoconstriction
- Hypoxemia
  - Impaired adaptation
Hyponatremia

- Step I: Is it real Hypotonic Hyponatremia? 
  – Yes it is !!

- Step II: Classification
  – Establish Volume status
Classification of Hyponatremia

**Hypovolemic**

- Hypotonic hyponatremia
  1. GI losses
  2. Skin losses
  3. Lung losses
  4. Third-space losses
  5. Renal losses-diuretics
  6. Cerebral salt wasting

**Hypervolemic**

- Hypotonic hyponatremia
  1. CHF
  2. Cirrhosis
  3. Nephrosis
  4. Kidney Failure

**Isovolemic**

- Hypotonic hyponatremia
  1. Water intoxication
  2. K+ losses
  3. Reset osmostat
  4. SIADH
  5. Impaired Adrenal or Thyroid function
  6. Drugs
    - sulfonylureas
    - carbamazepine
    - phenothiazines
    - antidepressants
Workup of Hyponatremia to Confirm Excess ADH
The 3 Essential Components!

<table>
<thead>
<tr>
<th>Serum Osmolality</th>
<th>Urine Osmolality</th>
<th>Urine Sodium</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Need to demonstrate true hypotonicity</td>
<td>• &gt; 100 mosm/L</td>
<td>• SIADH &gt; 30 meq/L</td>
</tr>
<tr>
<td>• &lt; 270 mosm/L</td>
<td>• Specific Gravity can also be used (&gt; 1.005)</td>
<td>• Hypovolemic or Hypervolemic &lt; 20 meq/L</td>
</tr>
</tbody>
</table>
**Appropriate Response to Hypotonicity**

Supraoptic / Paraventricular Nuclei

- Inhibit

ADH

- Specific Gravity $< 1.003$
- Dilute urine
- Osmolality $< 100$ mosm/L
Treatment of Hyponatremia

• **Key Questions**
  – Does the patient have symptoms?
    • Yes
    • No
  – How long has the hyponatremia been present?
    • Acute < 48 hours
    • Chronic > 48 hours
Correction of Hyponatremia

• Cellular Process of recovery from hyponatremia
  – Re-uptake of electrolytes (K, Phos)
  – Re-synthesis of organic osmolytes
  – *If the rate of correction exceeds the rate of re-accumulation of intracellular osmoles the cell will acutely shrink*

• Astrocytes / Oligodentrocytes are particularly sensitive to volume changes

• *Acute volume contraction of the cell causes it to stop producing myelin* - Apoptosis
Myelinolysis Syndromes

Central Pontine Myelinolysis (CPM)

Extra Pontine Myelinolysis (EPM)

Osmotic Demyelinating Syndrome (ODS)
Osmotic Demyelinating Syndrome

- **Clinical Sequence**
  - *Almost Always* associated with severe hyponatremia (Na < 120 meq/L)
  - Rapid correction of serum Na
    - > 10 meq/24 hours
  - Improvement of neurological symptoms for 2 – 6 days followed by the rapid development of
    - Confusion
    - Quadriplegia
    - pseudobulbar palsy
    - pseudo coma (‘locked-in syndrome’)
Osmotic Demyelinating Syndrome

Most common sites in order of frequency of involvement

- Pons
- Cerebellum
- Lateral geniculate body
- External capsule
- Extreme capsule
- Hippocampus
  - Putamen
  - Cerebral cortex/subcortex
- Thalamus
- Caudate nucleus

The following 10% or less:

- Claustrum
- Internal capsule
- Midbrain
- Internal medullary lamella
- Mamillary body
- Medulla oblongata
Osmotic Demyelinating Syndrome

CAT scan and/or MRI may not be Positive for Myelinolysis for up to 4 weeks after the event

Followup studies if the initial test is negative are mandatory
Osmotic Demyelinating Syndrome: Outcome

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>6%</td>
</tr>
<tr>
<td>Severely impaired</td>
<td>29%</td>
</tr>
<tr>
<td>Mildly impaired</td>
<td>32%</td>
</tr>
<tr>
<td>Full recovery</td>
<td>33%</td>
</tr>
</tbody>
</table>
Treatment of Hyponatremia

Avoid the Osmotic Demyelinating Syndrome
Hyponatremia: Treatment

Do not aggressively treat Chronic Hyponatremia

Acute

Cerebral Edema? < 48 hours

Symptomatic (Na < 130 meq/L)

Asymptomatic (Na < 120 meq/L)

3% Saline

Water restriction Oral Solute

Asymptomatic (Na 121 – 134 meq/L)
Treatment of Symptomatic Hyponatremic Encephalopathy

- 3% Saline
- 0.9 Normal Saline
- Vaptan
- Water Restriction
Hypertonic Saline (3%) and the Treatment of Hyponatremic Encephalopathy

- Na concentration of 513 meq/L
  - Compared to 154 meq/L in NS

- Two options for administration

**IV Bolus**
- 100-150 cc over 10-20 minutes
- Repeat x 3 until symptoms resolve

**IV Infusion**
- 125 cc/hr for 4 hrs or less if symptoms resolve
**Osmotic Demyelinating Syndrome**

- Correction rate of 1-2 meq/L/hr is acceptable in a patient with severe symptoms up to a total of 4 – 6 meq/L /day!
- Do not exceed > 8 meq/L increase in Na within a 24 hour period
Medical Options for Chronic Hyponatremia

- Water Restriction < 0.8 L/Day
- Increase Solute Intake
- Tolvaptan
- Avoid Thiazides / NSAIDs
- Urea
- Demeclocycline 300 mg BID
Vasopressin Receptors

**V1a**
- vascular smooth muscle
- platelets
- myometrium
- hepatocytes

**V1b**
- anterior pituitary

**V2**
- basolateral membrane
- collecting tubule
- vascular endothelium
- vascular smooth muscle

- vasoconstriction
- aggregation
- contraction
- glycogenolysis
- ACTH release
- AQP2 channel
- insertion and induction of AQP2 synthesis
- vWF and factor 8 release
- vasodilation
Vasopressin Antagonists - The Vaptans

<table>
<thead>
<tr>
<th>Agent</th>
<th>Receptor</th>
<th>Route</th>
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</thead>
<tbody>
<tr>
<td>Conivaptan</td>
<td>V1a + V2</td>
<td>IV</td>
</tr>
<tr>
<td>Lixivaptan</td>
<td>V2</td>
<td>oral</td>
</tr>
<tr>
<td>Tolvaptan</td>
<td>V2</td>
<td>oral</td>
</tr>
<tr>
<td>Satavaptan</td>
<td>V2</td>
<td>oral</td>
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</table>
ADH Mechanism

Cortical and Medullary Collecting Ducts

ADH

V2 receptor

Adenyl cyclase

Cyclic AMP

Aquaporin

Urea

NaCl

Medullary Interstitium

H2O

Urinary Space
Vaptans

Aquaretics ≠ Diuretics

Water loss only ≠ Sodium + Water loss
Response Rate of Serum Na to Tolvaptan

Average daily increase in serum Na 1.2 – 1.6 meq/L

This is unacceptably slow for the treatment of acute Hyponatremic Encephalopathy

Summary

Battle of the Guidelines for Acute Hyponatremia

European Guidelines

Vaptans are contraindicated
3% saline is the foundation of therapy

American Guidelines

Vaptans are permitted based on discretion of the physician
3% saline is the foundation of therapy
Tolvaptan for Chronic Hyponatremia

- Phase 3b, multicenter, randomized, double-blind, placebo-controlled, parallel-group pilot study
- 16 U.S. centers
- Titrated Tolvaptan to achieve a serum Na > 138 meq/L
- 3 week duration

*Verbalis J. Am J Kid Dis 2016 February*
- Na endpoint of 138 meq/L could only be achieved in 50%.
- Slight improvement in neurocognitive scores but not statistically significant.
- Improved bone mineralization.
- More long term data is required to support the use of Tolvaptan for chronic Hyponatremia.
Tolvaptan in CHF

No Improvement in Outcomes

Hyponatremia: Treatment

- Inhibition of Vasopressin
  - V2 receptor antagonists are now routinely available for the short term treatment of symptomatic chronic hyponatremia in the setting of hypervolemic or isovolemic hyponatremia. Contraindicated in patients with hypovolemic hyponatremia.
    - Will make the fluid deficit greater.
Tolvaptan

- Protein Bound
- CYP3A4 Metabolism
- 15% resistance in the Population
- Potential LFT increase
FDA
Tolvaptan is not approved beyond 30 days of continuous therapy due to potential hepatotoxicity
Don’t forget about…..Demeclocycline

**SYSTEMATIC REVIEW**

Evidence for the use of demeclocycline in the treatment of hyponatraemia secondary to SIADH: a systematic review


- Tetracycline derivative
- Results in ADH antagonism
- Dosed at 300mg BID to 600 mg BID
- Slow onset 3-5 days
- Adverse reactions
  - GI upset

Due to lack of data European Guidelines do not recommend Demeclocycline but if water restriction fails this remains a viable option.
And Don’t forget about ..... Urea

• Provides an osmotic diuretic that will improve water loss
• Oral solution to be used for chronic hyponatremia
<table>
<thead>
<tr>
<th></th>
<th>Na</th>
<th>K</th>
<th>Cl</th>
<th>HCO3</th>
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<tbody>
<tr>
<td>Current</td>
<td>125</td>
<td>3.5</td>
<td>90</td>
<td>20</td>
<td>6</td>
<td>0.5</td>
<td>90</td>
<td>257</td>
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<tr>
<td>Pre op</td>
<td>140</td>
<td>4.1</td>
<td>95</td>
<td>25</td>
<td>9</td>
<td>0.7</td>
<td>95</td>
<td>288</td>
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</table>

**Question**

- How would you describe her neurologic condition?
  
  A. Osmotic Demyelinating Syndrome with cerebral edema
  
  **B. Hyponatremic Encephalopathy with cerebral edema**
  
  C. Osmotic Demyelinating Syndrome with an acute decrease in cerebral volume
  
  D. Hyponatremic Encephalopathy with an acute decrease in cerebral volume
  
  E. Osmotic Demyelinating Syndrome with no change in brain volume
  
  F. Hyponatremic Encephalopathy with no change in brain volume
  
  G. Subdural hematoma secondary to Hyponatremia
  
  H. Acute CVA secondary to Hyponatremia
Question

• How much water can you (normal person) drink before you become hyponatremic?

A. 3 L
B. 6 L
C. 12 L
D. 18 L
E. 25 L
F. 30 L
G. With normal renal function the sky is the limit! Drink away! Last month I bought the unlimited drink package on a cruise ship and I got my money’s worth and my brain is fine (I think!)
### Question

- What is your target sodium level and how quickly should you correct symptomatic patients with hyponatremia to avoid seizures?

A. Correct up to a Na of 135 meq/L within 24 hours
B. Correct up to a Na of 130 meq/L within 24 hours
C. Correct no more than 15 meq/L within 24 hours
D. Correct no more than 12 meq/L within 24 hours
E. Correct no more than 10 meq/L within 24 hours
F. Correct no more than 8 meq/L within 24 hours

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**Na** - Sodium, **K** - Potassium, **Cl** - Chloride, **HCO3** - Bicarbonate, **BUN** - Blood Urea Nitrogen, **Cr** - Creatinine, **Glucose**, **Osm** - Osmolarity.
Final Hypotonic Hyponatremia

Rule # 3

Never correct Hyponatremia

➢ 4 – 6 meq/l in 24 hours
➢ (Maximum 8 meq/L)

ODS does not result from Hyponatremia

ODS results from the treatment of Hyponatremia
Hyponatremia is **not** a sodium problem

Hyponatremia is **a** water problem
Thank you!