Approach to the Hyponatremic Patient

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Disclosures

- Nothing to disclose

Learning Objectives

- Upon completion of this lecture you will be able to:
  - Understand the evaluation of a patient with hyponatremia
  - Determine the etiology of hyponatremia
  - Describe the important management principles for hyponatremia
  - Implement an evidence-based approach for the evaluation and treatment of hyponatremia

Outline

- Case Study
- Epidemiology
- Pathophysiology
- Treatment
- Cases

Case Study

- 49 year old female is admitted with hyponatremia and altered mental status. The 5 days prior to admission she was complaining of malaise and weakness. On the day of admission she became confused with decreased arousal. Vital signs are normal. Initially on arrival to the floor she was awake but now is minimally responsive, oriented x 0 and has slurred speech.

Case Study

- Labs reveal
  - Serum Na = 110 mEq/L
  - Urine Na = 75 mEq/L
  - Urine K = 45 mEq/L
  - Urine osm = 650 mosm/kg

Case Study

The best therapeutic approach would be to:

A. Restrict water intake to 1L/day
B. Give 1L normal saline
C. Give 1 to 2 ml/kg of 3% (hypertonic saline) for 2 to 3 hours
D. Give 15 mg of oral tolvaptan

Correct Answer: C give hypertonic saline

- Patient is experiencing neurologic symptoms so sodium needs to be changed by 4-6 mEq/L fairly quickly for symptoms to resolve
- Tolvaptan is not indicated when neurologic symptoms are present
- Fluid restriction is not appropriate given neurologic symptoms and will not work since Urine Na, Urine K and Urine Osm are so high

Case Study

The patient was given 1 L of Normal Saline over 5 hours. This approach will result in:

A. An increase in serum sodium
B. No change in serum sodium
C. A decrease in serum sodium

Correct answer: C, a decrease in serum sodium

- This patient has SIADH as determined by her high Urine Osm of 650 mosm/kg and high Urine Na
- In patients whose:

  Urine Na + Urine K > Serum Na the administration of normal saline will decrease sodium

Hyponatremia

- Most common electrolyte disturbance in hospitalized patients
  - Occurs in 30% of patients
- Results in increase morbidity, mortality and length of stay
- Wide variety of clinical symptoms
- Results from a varied spectrum of conditions
- Management remains problematic

Pathophysiology

- Defined as plasma Na^+ concentration below 135 meq/L
- Need to ask 2 questions to understand mechanism:
  - How do patients develop hyponatremia?
  - Why do they stay hyponatremic?

Generation of Hyponatremia

$$\text{Plasma } [Na^+] = \frac{\text{ECF } Na^+}{\text{ECF } H_20}$$

- From the formula, hyponatremia results from:
  - Either Na+ loss or water retention
- Results from relative excess of water
  - Solute loss occurs in a fluid isoosmotic to plasma
  - Key pathophysiological process at work is release of ADH

Water Handling in the Kidney

- Kidneys maintain serum osmolality within very narrow range 280-295 mOsm/kg
- Renal excretion of water is major factor controlling water metabolism
- Antidiuretic hormone (ADH; also called vasopressin) controls water excretion

Hyponatremia results from a defect in renal water excretion

- Excretion of free water is dependent on:
  - Normal function of the diluting segment
  - Normal delivery of tubular fluid to the distal diluting segment of the nephron
  - Absence of ADH
- Virtually ALL hyponatremic patients have an excess of ADH

ADH

- Secreted from posterior pituitary gland
- Osmotic and non-osmotic release

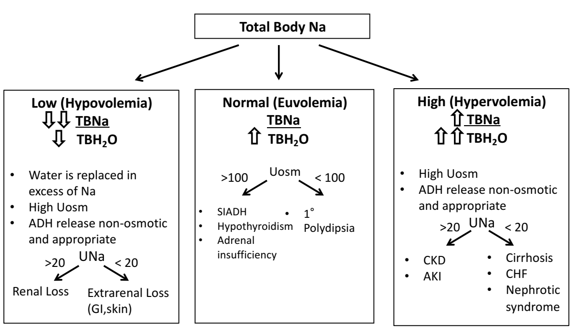
Osmotic release:

⇧ S_{osm}
↓
⇧ ADH
0.38 pg/ml for every 1 mOsm/kg increase in Sosm
↓
⇧ U_{osm}
ADH of 1 pg/mL causes U_{osm} of 225 mOsm/kg
↓
Reabsorption of water and return of S_{osm} back towards normal

Non-Osmotic Release of ADH

- ⇩ Effective intravascular blood volume stimulates ADH
- Non-osmotic release has priority
  – More important to maintain volume than tonicity
- ADH has a pressor effect (10% of MAP)

Decreases in serum Na indicate water is increased relative to total body Na



Classification of Hyponatremia

- Acute hyponatremia < 48 hours
- Chronic hyponatremia >48 hours or duration unknown
- Mild to moderate hyponatremia
  - Serum Na 121-135 meq/L
- Severe hyponatremia
  - Serum Na <120 meq/L

Signs and Symptoms

- Severity of symptoms is related to the rapidity and degree of reduction in SNa concentration
- Most patients are asymptomatic
- Neurologic complications more severe in menstruating women

Symptoms	Signs
Lethargy, apathy	Abnormal sensorium
Disorientation	Depressed deep tendon reflexes
Muscle cramps	Cheyne-Stokes respiration
Anorexia	Hypothermia
Nausea	Pathologic reflexes
Agitation	Pseudobulbar palsy
	Seizures

Treatment

- Rate of correction depends on severity of symptoms
- Overly rapid correction is harmful
- Goal in 24 hours: no more than 6-8 meq/L increase
- Goal in 48 hours: no more than 18 meq/L increase
- It is the daily change that matters, not the hourly change

Treatment

- Equations for calculating rates of treatment are just an estimate
  - Initially check serum Na every 4 hours
- Get urine electrolytes ASAP
- Follow urine output
- Serum Na can change rapidly so close monitoring is essential

Take home message

- In all settings, if correction of serum Na exceeds the accepted limits, re-lower the serum Na
- It is the daily change not the hourly change that matters

Case #1

- 30 y/o female with several days of vomiting and diarrhea. On presentation, mucous membranes are dry, BP is 80/40, pulse 120.
  - Serum Na = 110 meq/L
  - Uosm = 450 mosm/kg
  - UNa = < 10 meq/L
- Patient has hypovolemic hyponatremia due to non-osmotic release of ADH

Why is this patient likely to rapidly correct her sodium and what can you do about it?

- She is treated with several liters of normal saline and suddenly becomes polyuric.
  - Urine output is now 400 cc/hour
  - Serum Na has increased from 112 to 120 meq/L in 6 hours
  - UNa is now 20
  - UK is 20

You want to keep her serum Na at 120 meq/L for the next 18-24 hours, how do you this?

- Calculate her free water excretion
  - Urine output (volume) = Electrolyte clearance (C_E) + Free water clearance (C_{H2O})

So, C_{H20} = Volume – C_E

$$C_E = \frac{UNa + UK}{SNa} \text{ x volume}$$

$$C_E = \frac{20+20}{120} \times 400\text{cc/hour} = 133 \text{ cc/hr}$$

C_{H20} = Vol – C_E = 400 cc/hr- 133cc/hr = 267 cc/hr

So to maintain serum Na at 120 meq/L need to:

- Replace water loss in urine (267 cc/hour) + insensible losses
  - Insensible loss about 1000 cc/day = 42 cc/hour
- Patient needs 309 cc/hour of water (either drink it or in D5W) to keep Na at 120
  - If you give more than this, serum Na will drop
  - If you give less than this, serum Na will continue to increase

Now the patient is urinating >500 cc/hour and you are unable to keep up with her water losses and you are concerned her serum Na will increase. What else can you do?

Desmopressin (DDAVP) to stop the water diuresis

- ADH analog
- Safe and feasible
  - 20 hyponatremic patients whose trajectory was towards rapid correction
    - In 14 patients, DDAVP maintained correction rate in 24h
    - In 6 who had already exceeded rate in 24h, DDAVP prevented 48h goal of being exceeded

Perianayagam A, et al. CJASN 2008;3:331

Desmopressin

- Concentrates the urine
- 1 to 2 mcg IV Q6-8 hours
- Follow urine output
- Restrict free water intake (danger of dropping sodium too quickly)
  - May need some D5W back to bring sodium down

Is there anything else we could have done initially to prevent the rapid correction of her serum Na?

- Hypertonic saline + Desmopressin
  - 25 patients with serum Na < 120 meq/L
  - Desmopressin 1-2 mcg IV Q6-8 hours + 3% saline (dose calculated to increase SNa by 6 meq/L/24h)
  - Mean (SD) changes in serum Na in first 24 hours was 5.8 $\pm$ 2.8 meq/L
  - No patient corrected >12 meq/L in 24 hours
  - No adverse events

Sood et al. Am J Kidney Dis 2013;61:571

Limitations of DDAVP + 3% saline

- DDAVP prolongs the need for 3% saline
- Increased water intake can cause inadvertent decrease in Na
- Patients with marginal cardiac function may not tolerate the Na Load
- Does not address the excess in body water

Case # 2

- 50 y/o male with small cell carcinoma of the lung develops severe vomiting after the start of chemotherapy. On admission, mucous membranes are dry, BP is 105/60, pulse 110
  - Serum Na = 114 meq/L
  - Uosm = 498 mosm/kg
  - Urine Na = 6 meq/L
- Pt has hypovolemic hyponatremia

- The patient is treated with normal saline and the next morning his serum Na is 122 meq/L
- Should the normal saline be continued?
- Need to check urine lytes to find out
  - UNa <20 with Uosm >100 : pt still volume depleted and give more NS
  - UNa >20 with Uosm >100: pt now euvolemic with continued ADH release that is inappropriate (SIADH)

What do his urine tests tell us?

- Urine labs are back and show:
  - Uosm = 600 mosm/kg
  - UNa = 83 meq/L
  - UK= 45 meq/L
  - Urine output over past 24 hours: 1000 mL
- He has SIADH!!

How do I know if fluid restriction will work in my patient with SIADH?

- How much can he drink without becoming more hyponatremic?
  - Nothing
  - 1000 cc/day
  - 2000 cc/day
  - 3000 cc/day

Answer: 1000 cc/day

- He can drink the amount of free water lost each day (renal excretion + insensible loss)
  - C_{H20} = Volume – C_E
  - $C_E = \frac{UNa+UK}{SNa}$ x volume = $\frac{83+15}{122}$ x 1000cc/day = 1000cc/d
  - C_{H20} = 1000cc/day-1000cc/day= 0 cc/day
  - He has no free water excretion!
  - He can only drink his insensible losses (~ 1000cc/day)
  - To increase his SNa he has to be fluid restricted to <1000 cc/day

What would happen if we gave this patient 1L normal saline?

- Serum Na would fall
  - The excess NaCl will be excreted in a small amount of urine (513 ml)
    - Uosm 600 mosm/kg so: 308 mosmol/600mosm= 513 ml
  - All of the solute is excreted BUT nearly half of the water is retained

Effect of isotonic saline and hypertonic saline in SIADH with Uosm 600 mosm/kg

	NaCl (mosmol)	H_2O (mL)
Isotonic Saline		
In	308	1000
Out	308	513
Net	0	+ 487
Hypertonic Saline		
In	1026	1000
Out	1026	1700
Net	0	- 700

Take home message

- In patients whose UNa + UK > SNa the administration of normal saline will decrease sodium
  - Fluid restriction will not work in these patients
  - In this patient UNa + UK = 128, serum Na was 122

What else can we do to raise his serum Na since water restriction alone will not work?

- Need to increase his free water excretion
  - Furosemide
  - Urea
  - Demeclocycline
  - Vaptans

Furosemide

- Interferes with the countercurrent concentrating mechanism
- Results in water and salt losses
- Have to replace the salt (isotonic or hypertonic saline)
- Potassium repletion is needed
- Labor intensive treatment

Urea

- Osmotic diuresis and enhanced water excretion
- Dose 10-40 g/day
- Studies show corrects hyponatremia slowly
- Drawback is the taste
- Not routinely available in the United States

Demeclocycline

- Tetracycline antibiotic
- Decreases ADH signaling in collecting tubule
- Dose 300-600 mg twice a day
- Takes 2 to 4 days to begin working
- Can be nephrotoxic
- Corrects hyponatremia slowly
- Expensive ~ $20 per tablet

Vaptans

- ADH Receptors V1 and V2
  - V1 receptor: blood vessels and platelets (VWF)
    - Vasoconstriction
  - V2 receptor: Kidney collecting tubule
    - Water reabsorption
- Vaptans are selective V2 receptor antagonists
  - Tolvaptan (oral); conivaptan (IV)
- Only indicated for euvolemic or hypervolemic hyponatremia

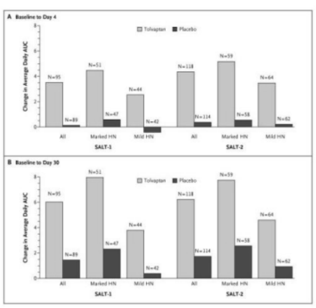
SALT Study

- 448 hyponatremic patients randomly assigned to placebo vs. tolvaptan
  - Tolvaptan 15mg/day titrated to max of 60mg/day
- Endpoint: change in the AUC for the serum Na level from baseline

Schrier et al. NEJM 2006;355:2099

Tolvaptan was successful in increasing the serum sodium concentrations

Change in the Average Daily Area under the Curve (AUC) for the Serum Sodium Concentration from Baseline to Day 4 (Panel A) and from Baseline to Day 30 (Panel B)



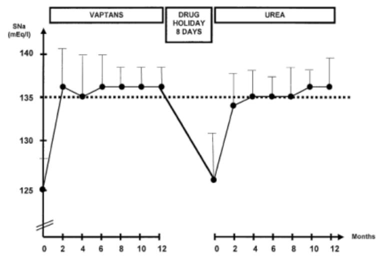
Schrier et al. NEJM 2006;355:2099

How does tolvaptan compare to usual therapies?

- Adult patients with well described SIADH
- Given vaptans for 12 months
- 8 day holiday period after 12 months
- Then started on oral urea (15-30gms/day)

Soupart et al. CJASN 2012;7:742

Vaptans and Urea have similar efficacy



Soupart et al. CJASN 2012;7:742

Dosing of Tolvaptan

- Start with 15mg daily, can increase to max of 60mg/day
- Follow urine electrolytes and urine output
- Monitor serum Na concentration closely (every 4 hours)
- Lift fluid restriction (allow patient ad lib fluids)
- When Na increases by 6-8 meq/L, match urine output with water

Limitations to Vaptans

- Should not be used for > 30 days
- Risk of liver toxicity
- Very expensive ($300 per tablet)
- Possibility of rapid correction of SNa
  - Must lift fluid restriction
  - Follow urine electrolytes and SNa closely
- Not indicated for neurologic symptoms

Case #3

- 68 yo male with PMH of HTN presents to the hospital with AMS. BP 150/80, pulse 70. Exam unremarkable. Upon arrival to the floor the patient has a tonic clonic seizure.
- Patient's weight= 80 kg
- Serum Na=114 meq/L.
- Uosm = 700 mosm/kg
- UNa = 95 meq/L

How do you determine how much hypertonic (3%) saline to give?

- Need to increase the serum Na by 4 -6 meq/L
  - Seizures should stop if this is achieved
- Hypertonic saline has 513 meq of Na
- Give 2 mL/kg bolus
  - For our patient this would be 160 mL.
  - If seizures or severe neurologic symptoms continue, another bolus can be given 1-2 more times

3% saline is also used for other severe neurologic symptoms

- Goal is to change Na by 4-6 meq/L
- Give 1 to 2mL/kg per hour for 2 to 3 hours
- Symptoms should improve

Take home message

- 3% saline should only be used for hyponatremic emergencies

Conclusions

- Hyponatremia is the most common electrolyte disorder
- Volume status, urine electrolytes and osmolality are used to identify etiology
- Monitor plasma Na^+, urine lytes and urine output
- Know when fluid restriction alone will not work
- Know when normal saline will worsen the hyponatremia

Conclusions

- Rate of correction depends on symptoms
- Neurologic symptoms should improve when SNa is changed by 4-6 meq/L
- Hypertonic saline should only be used for hyponatremic emergencies
- Stay within accepted correction limits for first 24-48 hours
- If overcorrected, re-lower the serum Na