

Learning Objectives

- Describe the underlying pathophysiology, risk factors, and risk stratification of hospitalized patients with hyponatremia
- Identify the mechanisms in which hyponatremia complicates the management of chronic medical conditions
- Assess the pharmacist's role and current treatment options for hyponatremia in the hospital setting.
- Examine the role of vasopressin receptor antagonists in the management of hyponatremia in the hospitalized patient

PLEASE TAKE A MOMENT TO ANSWER THE PRE-ACTIVITY TEST QUESTIONS

Hyponatremia

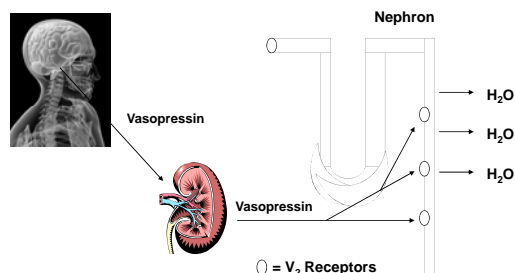
- **Most common electrolyte abnormality**
- **Associated with many systemic diseases**
 - Major: dilution of extracellular fluid
 - Minor: total body losses of sodium
- **Acute vs. Chronic**
 - Often duration is difficult to determine

Hyponatremia can be caused by dilution from retained water, or by depletion from electrolyte losses in excess of water

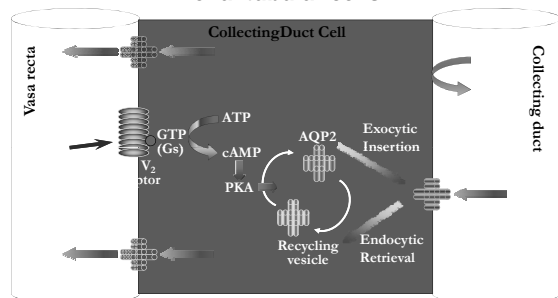
Role of Vasopressin

- **Vasopressin = ADH = antidiuretic hormone**
- **Physiologic sodium/water balance**
 - Thirst: stimulated by rise in osmolality
 - Osmoreceptors
 - Water excretion: regulated by vasopressin
 - Osmoreceptors
 - \uparrow Osmolality = \uparrow vasopressin secretion = \uparrow H₂O reabsorption
 - \downarrow Osmolality = \downarrow vasopressin secretion = \downarrow H₂O reabsorption

Role of Vasopressin



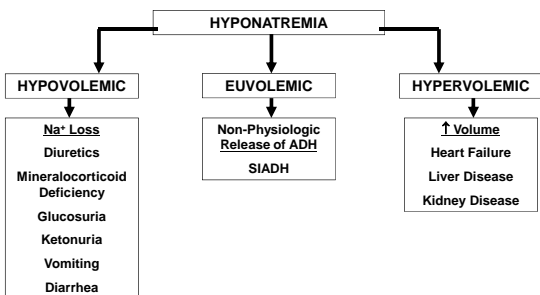
AVP regulation of water reabsorption from renal tubular cells



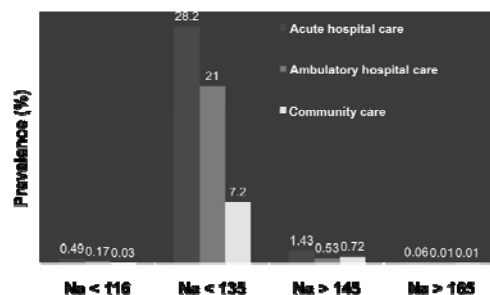
Classification: Osmolality

- **Hypotonic hyponatremia**
 - Sodium directly related to osmolality
 - Most cases
- **Isotonic/Hypertonic hyponatremia**
 - Pseudohyponatremia
 - Non-sodium solutes increase osmolality
 - Glucose
 - \uparrow osmolality \rightarrow fluid shifts \rightarrow dilution of sodium

Classification: Volume Status



Prevalence of dysnatremias at initial presentation to a health care provider (data from 303,577 samples on 120,137 patients available for analysis)



Adapted from: Hawkins RC. Clin Chim Acta. 2003; 337(1-2):169-72.

Drug-Related Causes

Sodium Loss

- Diuretics

↑ Vasopressin/ADH effects

- Antipsychotics
- Antidepressants
- DDAVP
- Oxytocin

Risk Stratification

- **Acute vs. Chronic**
 - Acute = less than 48 hours in duration
 - Concerned about neurologic sequelae
 - Osmotic differential between brain and blood
 - Brain swelling
 - Chronic = greater than 48 hours in duration
 - Symptoms may be more modest
 - Brain has time to adapt
- **Duration of hyponatremia**
 - How aggressive?
 - How fast?

Discussion Question

Common symptoms of chronic hyponatremia include fatigue, nausea, dizziness, lethargy, confusion, and gait disturbances?

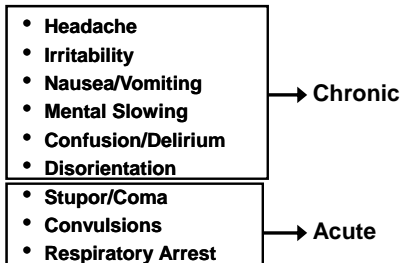
- A. True
B. False

Discussion Question - ANSWER

Common symptoms of chronic hyponatremia include fatigue, nausea, dizziness, lethargy, confusion, and gait disturbances?

- A. True
B. False

Symptomatic Hyponatremia: Neurological Manifestations



Symptoms Associated with Chronic Hyponatremia

- Malaise/Lethargy: 109 (49%)
- Dizzy Spells: 104 (47%)
- Vomiting: 77 (35%)
- Confusion/Obtundation: 39 (17%)
- Falls: 37 (17%)
- Headache: 13 (6%)
- Seizures: 2 (0.9%)

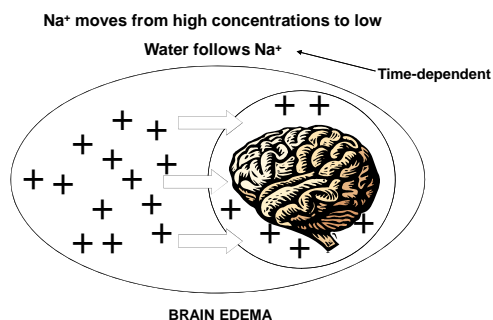
223/223 resolved symptoms with correction of [Na⁺] via cessation of thiazide treatment

Increased Risk of Falls with “Asymptomatic” Hyponatremia

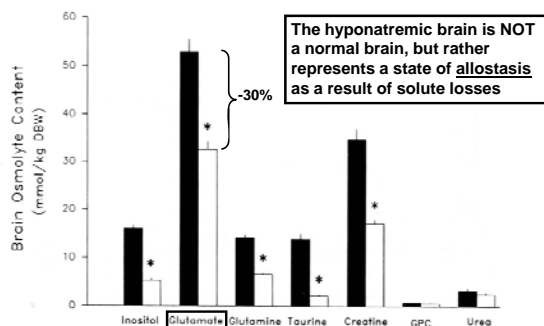
Group	n	Falls	Odds Ratio	Adjusted Odds Ratio*
“Asymptomatic” Chronic Hyponatremia	122	21.3%	9.45 (2.64-34.09) $p < .001$	67.43 (7.48-607.42) $p < .001$
Normonatremic controls	244	5.35%	1.00	1.00

Adapted from: Renneboog B, et al. *Am J Med.* 2006;119(1): 71. e1-8.

Sodium and the Brain



Reductions of Brain Organic Osmolytes after 14 days of Sustained Hyponatremia



* $P < 0.01$ compared to normonatremic control rats. Adapted from: Verbalis JG, et al. *Brain Res.* 1991; 567(2):274-82.

Discussion Question

There is less likelihood of rapid fluid shifts and brain edema in cases of acute hyponatremia than there are in cases of chronic hyponatremia

- A. True
- B. False

Discussion Question - ANSWER

There is less likelihood of rapid fluid shifts and brain edema in cases of acute hyponatremia than there are in cases of chronic hyponatremia

- A. True
- B. False

Acute vs. Chronic and the Brain

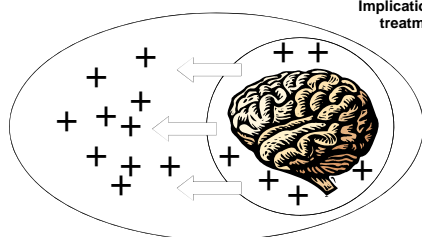
- **Acute hyponatremia**
 - Rapid onset
 - Greater likelihood of rapid fluid shifts and brain edema
- **Chronic hyponatremia**
 - Insidious onset
 - Less likelihood for brain edema
 - Time for compensatory increases in organic osmolytes

Sodium and the Brain

Na⁺ moves from high concentrations to low

Water follows Na⁺

Implications for treatment



Rapid fluid shifts out of the brain: OSMOTIC DEMYELINATION

How Aggressive? How Fast?

LEVEL 3 - SEVERE SYMPTOMS:

vomiting, seizures, obtundation, respiratory distress, coma

→ **Emergency!**
Correct RAPIDLY

LEVEL 2 - MODERATE SYMPTOMS:

nausea, confusion, disorientation, altered mental status

LEVEL 1 - NO OR MINIMAL SYMPTOMS:

headache, irritability, inability to concentrate, altered mood, depression

→ **OK to correct more slowly**

Hyponatremia and Heart Failure

Implications of Hyponatremia

Heart failure

- There are an estimated 7 million Americans with HF (2% of US population).
- Hyponatremia is one of the newer and emerging risk factors for an adverse prognosis in chronic heart failure
- Increased release of vasopressin may result in excess fluid retention and hyponatremia.

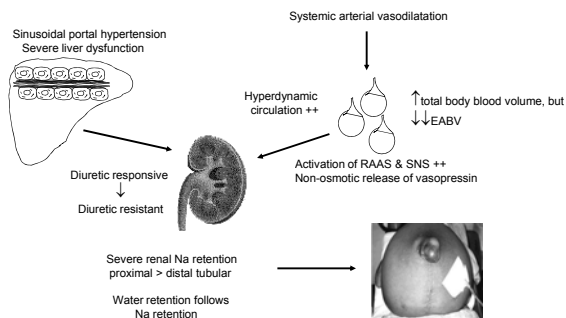
Hyponatremia and Liver Disease

Implications of Hyponatremia

Liver Disease

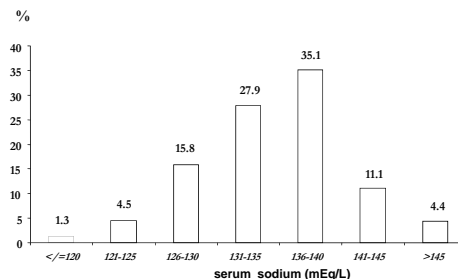
- Associated with poor prognosis & reduced survival
- Impairs the management of ascites
- Predisposes to hepatic encephalopathy
- Impairs quality of life

Pathogenesis of Hyponatremia in Cirrhosis



When water retention > Na retention, hyponatremia develops

Distribution of serum sodium in patients with liver cirrhosis & ascites (n=983)



Adapted from P. Angeli et al. *Hepatology* 2006; 44:1535-1542

Serum Sodium and Mortality

Liver Transplant candidates in the VA system, 97-03 (n= 507)

- Hepatitis C (68%), EtOH (67%)
- MELD 16.2 ± 6.7
- Hyponatremia (<130 mEq/L): 31%
- Persistent Ascites/Hydrothorax: 38%

Predictors of 6-month mortality

	Odds Ratio	p
MELD	1.25 (1.16-1.35)	<0.001
Na < 135 mEq/L	2.76 (1.31-5.81)	0.008
Persistent Ascites	2.72 (1.31-5.71)	0.008

Heuman DM, et al. *Hepatology*, 2004;40(4):802-10.

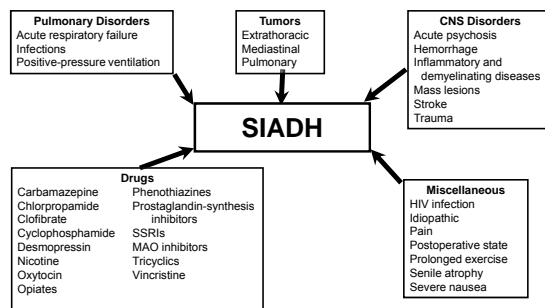
Syndrome of inappropriate antidiuretic hormone (SIADH) secretion

Syndrome of Inappropriate Anti-diuretic Hormone (SIADH): Essential Criteria

- True plasma hypoosmolality
- Urine concentration inappropriate for plasma osmolality ($U_{osm} > 100 \text{ mOsm/kg H}_2\text{O}$)
- Clinical euvoolemia, no diuretic therapy
- Absent renal sodium conservation ($U_{Na} > 30 \text{ mmol/L}$)
- Normal thyroid, adrenal and renal function

Bartter FC, et al. *Am J Med*. 1967; 42:790-806.

Causes of Syndrome of Inappropriate Anti-diuretic Hormone (SIADH):



Conclusions

- Hyponatremia is a common disorder of electrolytes seen in the hospital setting.
- Acute severe hyponatremia can cause substantial morbidity and mortality, particularly in patients with co morbidities.
- Overly rapid correction of chronic hyponatremia can cause severe neurologic deficits and death.
- SIADH is the most common cause of euvolemic hyponatremia in clinical medicine.
- Hypervolemic Hyponatremia is a common occurrence in patients with cirrhosis, particularly those with advanced chronic disease.
- Early diagnosis and intervention can improve outcomes in these patients SIADH and cirrhosis .

Discussion Question

Which of the following medications is relatively contraindicated in the treatment of patients with cirrhosis because of a high incidence of nephrotoxicity?

- A. Conivaptan
- B. Tolvaptan
- C. Demeclocycline
- D. Spironolactone

Discussion Question - ANSWER

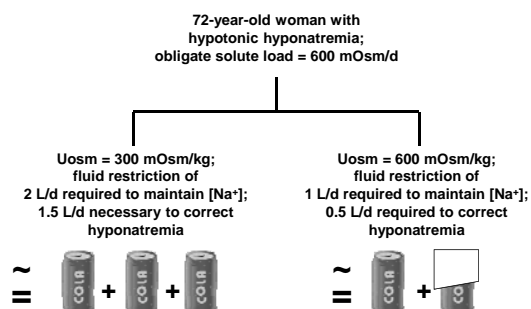
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- A. Conivaptan
- B. Tolvaptan
- C. Demeclocycline
- D. Spironolactone

Current Treatment Strategies

AGENT	LIMITATIONS
Fluid restriction	<ul style="list-style-type: none"> • Slow to correct over days (1-2 mEq/L/day) • Poorly tolerated due to thirst • Should not be used with high AVP level and urine osmolality
Diuretics	<ul style="list-style-type: none"> • Allows relaxation of fluid restriction • Potential for ototoxicity, volume depletion, and K⁺ and Mg⁺ depletion
Demeclocycline	<ul style="list-style-type: none"> • Not FDA approved for hyponatremia • Slow to correct over days • Nephrotoxic in cirrhosis and heart failure
Lithium	<ul style="list-style-type: none"> • Slow to correct • Must monitor serum levels • CNS side effects, cardiotoxic, GI disturbances

Urine Concentration Determines the Stringency of Water Restriction



Current Treatment Strategies

AGENT	LIMITATIONS
Isotonic saline	<ul style="list-style-type: none"> • Ineffective in dilutional hyponatremia • Should not be used in setting of edema • No safety data • Complex calculations
Hypertonic saline	<ul style="list-style-type: none"> • No consensus regarding appropriate infusion rates • Overcorrection can cause osmotic demyelination syndrome • Should not be used in setting of edema • No safety data • Complex calculations

Hypertonic Saline Considerations

- **Use equations to calculate rate/duration**
 - Medication safety issues?
- **7.1 mEq/L in 24 hours**
- **10% rate of overcorrection**
 - Higher risk for overcorrection when $\text{Na}^+ < 120 \text{ mEq/L}$

Adroque, et al. *N Engl J Med* 2000;342:1581-9.
Mohmand, et al. *Clin J Am Soc Neph* 2007;2:1110 - 7.

Overcorrection Defined

- **Increase in Na^+**
 - Within 24 hours
 - $>10 - 12 \text{ mEq/L}$
 - Within 48 hours
 - $>18 \text{ mEq/L}$

Verbalis JG, et al. *Am J Med* 2007; 120:S1-S21
Mohmand, et al. *Clin J Am Soc Neph* 2007;2:1110 - 7

Newest Option for Hyponatremia: Vasopressin Antagonists

Patient Case: Asymptomatic Hyponatremia

- 75-yo female, stable CHF and type 2 DM
- Fell while coming down the stairs in herhouse, now severe leg pain, pleuritic chest pain, SOB
- ER: left hip fracture, multiple rib fractures, small pleural effusions bilaterally, no pneumothorax
- Admitted to ICU for monitoring, physical exam: patient is awake and oriented; blood pressure is 130/80; no focal neurological deficits; bibasilar rales; point Tenderness over rib cage

Patient Case: Asymptomatic Hyponatremia

Labs:

$\text{Na} = 128$, $\text{K} = 3.4$, $\text{Cl} = 104$, $\text{HCO}_3 = 24$
glucose = 185, BUN = 20, Cr = 1.3
Hct = 36

Posm = 275, Uosm = 350, $\text{UNa}^+ = 60$

$\text{O}_2 \text{ sat} = 90\%$ room air

Discussion Question

Is this patient a candidate for vasopressin antagonist therapy for hyponatremia?

- A. Yes
- B. No

Discussion Question - ANSWER

Is this patient a candidate for vasopressin antagonist therapy for hyponatremia?

- A. Yes
- B. No

What do they do?

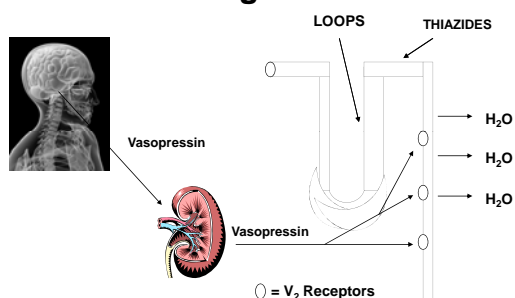
Diuresis:

increased excretion of urine by the kidney; includes water and typically increased solute excretion as well

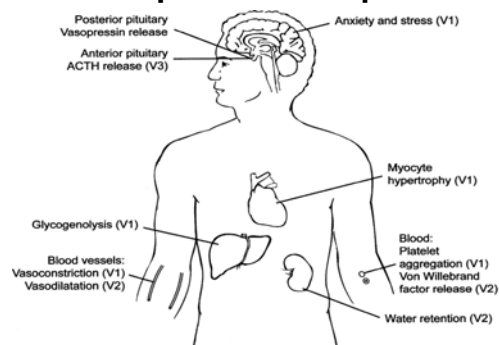
Aquaresis:

increased excretion of water by the kidney without increased solute, i.e., electrolyte-sparing excretion of free water by the kidney

Mechanism of Vasopressin Antagonists



Vasopressin Receptors



Non-peptide AVP receptor antagonists

	Conivaptan	Lixivaptan	Satavaptan	Tolvaptan
Receptor	V _{1a} /V ₂	V ₂	V ₂	V ₂
Route of administration	IV	Oral	Oral	Oral
Urine volume	↑	↑	↑	↑
Urine osmolality	↓	↓	↓	↓
Na ⁺ excretion/ 24 hrs	↔	↔ low dose ↑ high dose	↔	↔

FDA Approved

Lee CR, et al. *Am Heart J* 2003;146:9-18.

CONIVAPTAN

Conivaptan: Pivotal Phase III Trial

- **R, MC, DB, PC**
 - n = 84 patients
- **4 day continuous infusion**
 - Placebo
 - Conivaptan 40mg/day
 - Conivaptan 80mg/day
- **Primary endpoint**
 - Δ in serum sodium from baseline (AUC)
- **Secondary endpoints**
 - Time from 1st dose to sodium \geq 4mEq/L, time sodium \geq 4mEq/L from baseline, # patients with \geq 6mEq/L increase in sodium or normal (\geq 135mEq/L).

Zeltser D, et al. *Am J Nephrol* 2007;27:447-57.

Patient Population

- **Inclusion criteria**
 - Age > 18 years
 - Serum Na⁺ = 115 – 130mEq/L
 - Posm < 290mOsm/kg
 - Fasting BG < 275mg/dl
 - Euvolemic or hypervolemic
- **Exclusion criteria**
 - Hypovolemic hyponatremia
 - Uncontrolled HTN, bradyarrhythmia or tachyarrhythmias
 - Medications interact with CYP3A4
 - Emergent treatment for hyponatremia

Zeltser D, et al. *Am J Nephrol* 2007;27:447-57.

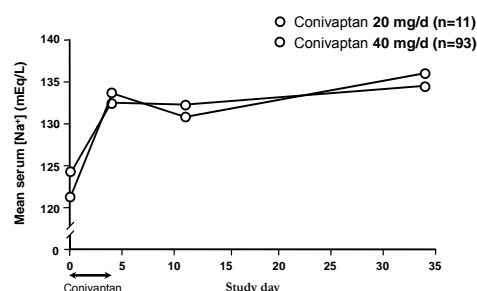
RESULTS

Endpoint	Placebo N = 29	Con 40mg IV N = 29	Con 80mg IV N = 26
Δ in baseline Na AUC, mean (SE), mEq ^h /L	12.9 (61.2)	490.9 (56.8) †	716.6 (60.4) †
Time 1 st dose to Na \geq 4mEq/L from BL, median hrs (95% CI)	NE	23.7 (95%CI 10.0, 24.0) †	23.4 (95%CI 6.0, 24.0) †
Total time serum Na above baseline, mean (SE), h	14.2 (5.25)	53.2 (5.17) †	72.7 (5.43) †
Change in Na from baseline to end of treatment, mean (SE), mEq/L	0.8 (0.80)	6.3 (0.74) †	9.4 (0.79) †
Increase Na \geq 6mEq/L or > 135mEq/L, n (%)	6 (20.7%)	20 (69.0%) †	23 (88.5%) †

† p < 0.001, NE = not estimable

Zeltser D, et al. *Am J Nephrol* 2007;27:447-57.

Conivaptan: open label extension study

Conivaptan hydrochloride injection.
Prescribing information; February 2006.

Conivaptan Adverse Events

	Placebo (n=29)	Con 40 mg (n=29)	Con 80 mg (n=26)
Phlebitis	6.9%	24.1%	30.8%
Hypotension	6.9%	13.8%	19.2%
Postural Hypotension	0%	13.8%	3.8%
Injection Site Inflammation	0%	6.9%	11.5%
Pyrexia	0%	10.3%	7.7%
Hyperkalemia	3.4%	0%	
Injection-site Thrombosis	0%	10.3%	0%
Overcorrection	0%	6.9%	7.7%

Zeltser D, et al. *Am J Nephrol* 2007; 27: 447-457.

Special Populations: Heart Failure

- **Do not use to TREAT heart failure**
 - No benefit
 - No worsening of heart failure
- **Risk of adverse effects must be outweighed by anticipated benefits of increasing sodium**

Special Populations: Neurology

2 retrospective case series, neuro ICU patients

Series	n	Dosing	Timing	6mEq/L Rise	Safety
#1	22	Bolus + Infusion	24 hrs	86% 24h post D/C = 47%	No excessive correction 5 pts with phlebitis
#2	24	Bolus only*	72 hrs	Single Bolus: 56% Double Bolus: 52%	1 pt with excessive correction No phlebitis

*Concomitant 1.25% or 2% saline permitted

Wright, et al. *Neurocritical Care* 2009;11:8-13
Murphy T, et al. *Neurocritical Care* 2009;11:14-19

Conivaptan: Practical Considerations

- **20 mg IV over 30 minutes, then 20 mg continuous IV infusion over 24 hours**
 - May increase to 40 mg daily if inadequate response
 - Administer x 1 to 3 days
 - Only compatible with 5% dextrose.
 - Limited data on IV drug-drug compatibility.
 - To minimize the risk of vascular irritation
 - Administer through large veins
 - Change infusion site every 24 hours
- **Contraindication: Co-administration with potent CYP3A4 enzyme inhibitors**
 - ketoconazole, itraconazole, indinavir

Conivaptan hydrochloride injection. Prescribing information. February 2006.

Discussion Question

The V2 receptor is associated with which of the following actions?

- A. Vasoconstriction
- B. Vasodilation
- C. Water retention
- D. Both B & C

Discussion Question - ANSWER

The V2 receptor is associated with which of the following actions?

- A. Vasoconstriction
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- C. Water retention
- D. Both B & C

TOLVAPTAN

SALT – 1 and SALT – 2

Study of Ascending Levels of Tolvaptan in Hyponatremia

- **Two MC, R, DB, PC trials**
 - Tolvaptan 15 mg (increased to 30 – 60 mg)
 - Placebo
- **Primary Endpoints:**
 - Δ in AUC for the serum Na^+ concentration
 - Baseline to day 4
 - Baseline to day 30

Schrier RW, et al. *NEJM* 2006; 355(20):2099 -2112.

SALT – 1 and 2 Patient Population

- **Inclusion criteria**
 - > 18 years of age
 - Sodium < 135
 - CHF
 - Cirrhosis
 - SIADH
- **Exclusion criteria**
 - Hypovolemic hyponatremia
 - Cardiac surgery, MI, SVT, angina, CVA, Pulmonary HTN
 - Hypotension, Uncontrolled diabetes mellitus
 - SCr > 3.5mg/dl
 - Child-Pugh > 10

Schrier RW, et al. *NEJM*. 2006; 355(20):2099 -2112.

SALT – 1 RESULTS

AUC for serum Na⁺ (mmol/L)

Endpoint	Placebo n = 103	Tolvaptan n = 103	p-value
All Patients: Day 4	0.25 ± 2.08	3.62 ± 2.68	< 0.001
All Patients: Day 30	1.66 ± 3.59	6.22 ± 4.10	< 0.001
Mild (130 – 135 mmol/L): Day 4	- 0.32 ± 2.27	2.52 ± 1.95	< 0.001
Mild (130 – 135 mmol/L): Day 30	0.68 ± 2.78	3.87 ± 3.01	< 0.001
Marked (< 130 mmol/L): Day 4	0.76 ± 1.77	4.56 ± 2.88	< 0.001
Marked (< 130 mmol/L): Day 30	2.54 ± 4.01	8.24 ± 3.84	< 0.001

SALT – 2 Data not shown but similar

Note: Na⁺ concentration similar to placebo within 5 days of D/C

Schrier RW, et al. *NEJM*. 2006; 355(20):2099 -2112.

Special Populations: Heart Failure

EVEREST TRIALS: Short-term

- **2 identical short term trials**
- **R, DB, PC, MC**
- **Patients:**
 - Hospitalized for HF, EF < 40%, HF symptoms
 - Not required to have HYPONATREMIA
- **Treatment**
 - Tolvaptan 30 mg daily
 - Placebo
- **Primary Endpoint**
 - Global clinical status and body weight
 - Discharge or 7 days

Gheorghade M, et al. *JAMA* 2007;297:1332-43.

Special Populations: Heart Failure

EVEREST TRIALS: Long-term Outcomes

- **Extension of short term trials**
- **Minimum 60 day treatment (median = 9.9 mos)**
 - Tolvaptan/Placebo
 - On top of standard HF therapy
- **Primary Endpoint**
 - All-cause mortality
 - Superiority/Non-inferiority
 - Composite: CV death or hospitalization for HF
 - Superiority
- **Secondary Endpoint**
 - Δ in dyspnea, body weight, edema

Konstam MA, et al. *JAMA* 2007;297:1319-31.

Special Populations: Heart Failure

EVEREST TRIALS: Results

The Endpoints

Short – term results

- Global clinical status and body weight
 - Improvement with tolvaptan

Long – term results

- All-cause mortality
 - No difference
- Composite: CV death or hospitalization for HF
 - No difference
- Δ in dyspnea, body weight, edema
 - Improvement with tolvaptan

Konstam MA, et al. *JAMA* 2007;297:1319-31
Gheorghade M, et al. *JAMA* 2007;297:1332-43

Tolvaptan: Practical Considerations

- **Indicated for symptomatic hyponatremia**
 - < 125mEq/L
 - Unresponsive to correction with fluid restriction
 - In-hospital initiation
- **Administered by oral route once daily**
 - 15 mg/30 mg/60 mg
- **Contraindication: Co-administration with potent CYP3A4 enzyme inhibitors**
 - ketoconazole, itraconazole, indinavir
- **Patients should be encouraged to drink when thirsty**
- **Co-administration with hypertonic saline: NR**

Tolvaptan [package insert]; 2009.

Tolvaptan Adverse Effects

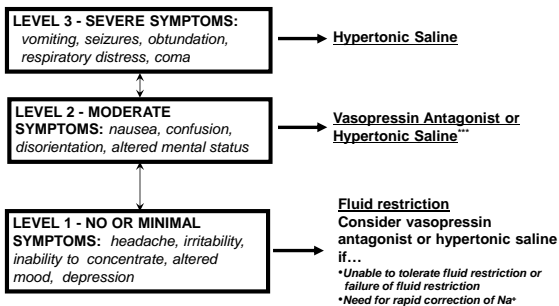
SALT studies

- No osmotic demyelination
- Excessive Na⁺ correction = 1.8%

EVEREST

- Thirst
- Polyuria
- Pollakiuria
- Hyponatremia

HYPONATREMIA TREATMENT OPTIONS



Vasopressin Antagonist Formulary Considerations

- **Vasopressin antagonist vs. Hypertonic Saline?**
 - Unable to tolerate fluids
 - Degree of hyponatremia
- **Restrict to a specific service?**
 - Endocrine, nephrology, hepatology?
- **Tolvaptan and insurance status**
 - Reversible effect on sodium upon discontinuation

Conclusions

- **Considerations in Management**
 - Pathophysiology/Classification
 - Symptoms (Type, Severity, Duration, Onset)
 - Underlying disease states
- **Primary treatment options**
 - Fluid restriction, Hypertonic saline, Vasopressin receptor antagonists
- **Role of the pharmacist**
 - Global policies related to use
 - Agent selection
 - Monitoring

PLEASE TAKE A MOMENT TO ANSWER
THE POST-ACTIVITY TEST QUESTIONS

