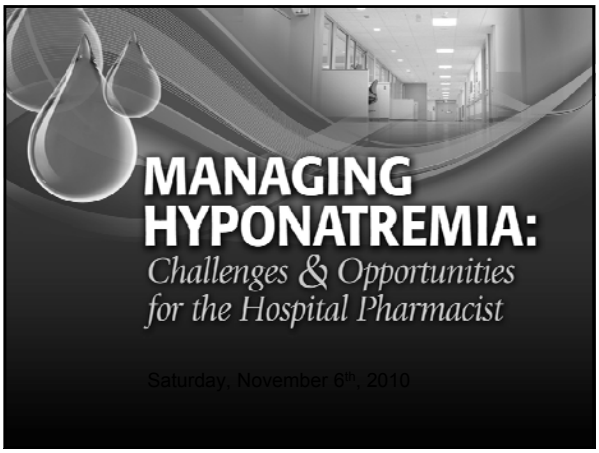
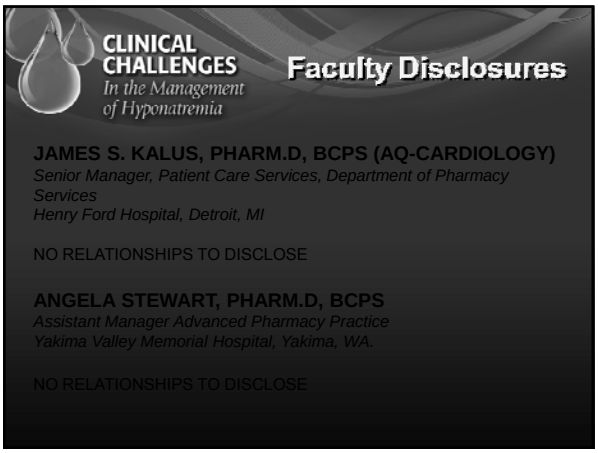




Learning Objectives

- 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 pharmacists 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

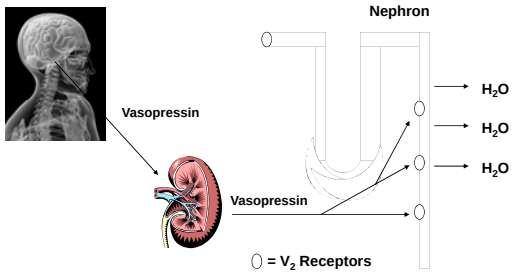
- **Most common electrolyte abnormality**
- **Associated with many systemic diseases**
  - Major: dilution of extracellular fluid
  - Minor: total body losses of sodium
- **Acute vs. Chronic**
  - Often duration is difficult to determine

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

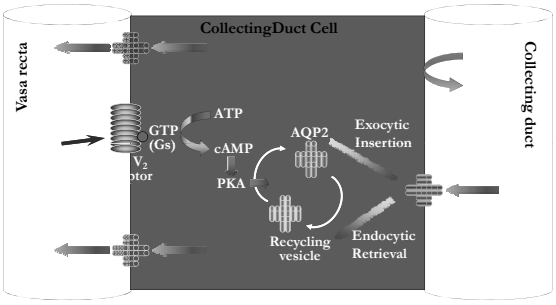
Role of Vasopressin

- **Vasopressin = ADH = antidiuretic hormone**
- **Physiologic sodium/water balance**
  - Thirst: stimulated by rise in osmolality
    - Osmoreceptors
  - Water excretion: regulated by vasopressin
    - Osmoreceptors
      - ↑ Osmolality = ↑ vasopressin secretion = ↑ H_2O reabsorption
      - ↓ Osmolality = ↓ vasopressin secretion = ↓ H_2O reabsorption

Role of Vasopressin



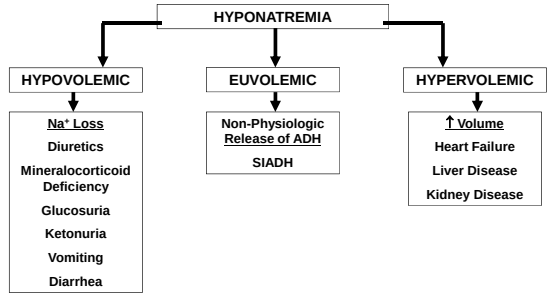
AVP regulation of water reabsorption from renal tubular cells



Classification: Osmolality

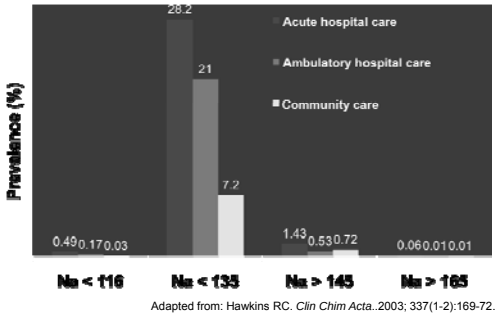
- **Hypotonic hyponatremia**
  - Sodium directly related to osmolality
  - Most cases
- **Isotonic/Hypertonic hyponatremia**
  - Pseudohyponatremia
  - Non-sodium solutes increase osmolality
    - Glucose
    - ↑ osmolality → fluid shifts → dilution of sodium

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 sequellae
      - 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

- **Headache**
- **Irritability**
- **Nausea/Vomiting**
- **Mental Slowing**
- **Confusion/Delirium**
- **Disorientation**

→ **Chronic**

- **Stupor/Coma**
- **Convulsions**
- **Respiratory Arrest**

→ **Acute**

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%)**

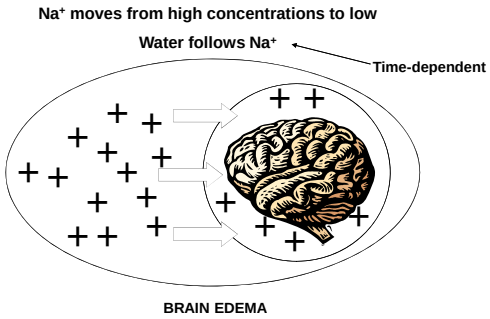
223/223 resolved symptoms with correction of $[Na^+]$ via cessation of thiazide treatment

Increased Risk of Falls with "Asymptomatic" Hyponatremia

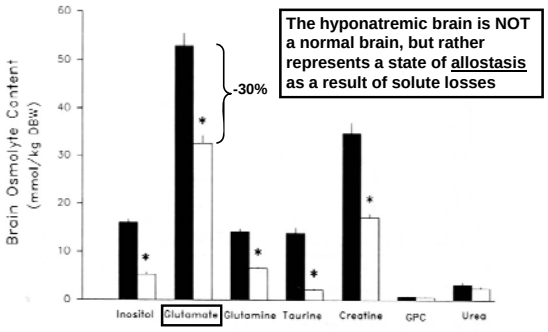
Group	n	Falls	Odds Ratio	Adjusted Odds Ratio*
"Asymptomatic"Chronic Hyponatremia	122	21.3%	9.45 (2.64-34.09) p <.001	67.43 (7.48-607.42) p <.001
Normonatremic controls	244	5.35%	1.00	1.00

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



The hyponatremic brain is NOT a normal brain, but rather represents a state of allostasis as a result of solute losses

*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

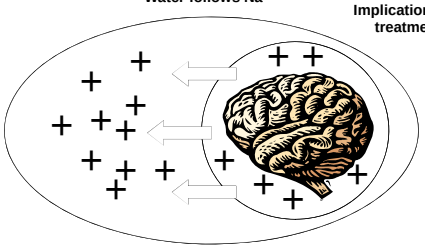
- **Acute hyponatremia**
  - Rapid onset
  - Greater likelihood of rapid fluid shifts and brain edema
- **Chronic hyponatremia**
  - Insidious onset
  - Less likelihood for brain edema
    - Time for compensatory increases in organic osmolytes

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.

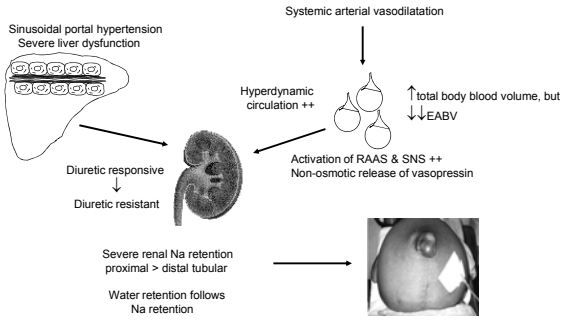
Hyponatremia and Liver Disease

Implications of Hyponatremia

Liver Disease

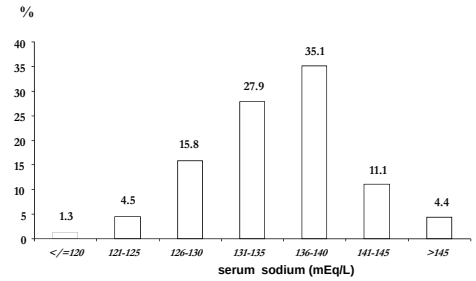
- Associated with poor prognosis & reduced survival
- Impairs the management of ascites
- Predisposes to hepatic encephalopathy
- Impairs quality of life

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.

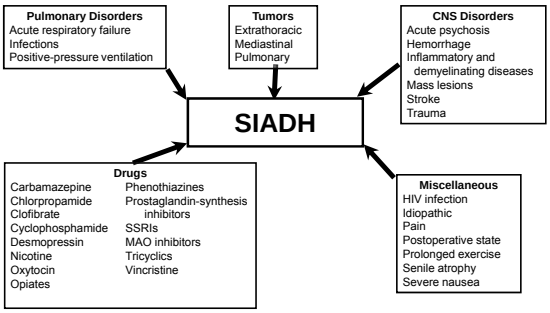
Syndrome of inappropriate antidiuretic hormone (SIADH) secretion

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

- True plasma hypoosmolality
- Urine concentration inappropriate for plasma osmolality (U_{osm} > 100 mOsm/kg H_2O)
- Clinical euvolemia, no diuretic therapy
- Absent renal sodium conservation (U_{Na} > 30 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

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

Current Treatment Strategies

AGENT	LIMITATIONS
Fluid restriction	• 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	• Allows relaxation of fluid restriction • Potential for ototoxicity, volume depletion, and K^+ and Mg^+ depletion
Demeclocycline	• Not FDA approved for hyponatremia • Slow to correct over days • Nephrotoxic in cirrhosis and heart failure
Lithium	• Slow to correct • Must monitor serum levels • CNS side effects, cardiotoxic, GI disturbances

Urine Concentration Determines the Stringency of Water Restriction

72-year-old woman with hypotonic hyponatremia; obligate solute load = 600 mOsm/d

Uosm = 300 mOsm/kg; fluid restriction of 2 L/d required to maintain $[Na^+]$; 1.5 L/d necessary to correct hyponatremia

Uosm = 600 mOsm/kg; fluid restriction of 1 L/d required to maintain $[Na^+]$; 0.5 L/d required to correct hyponatremia

Current Treatment Strategies

AGENT	LIMITATIONS
Isotonic saline	• Ineffective in dilutional hyponatremia • Should not be used in setting of edema • No safety data • Complex calculations
Hypertonic saline	• 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 Na^+ < 120 mEq/L

Adrogue, 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 mEq/L
  – Within 48 hours
    - >18 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:

Na = 128, K = 3.4, Cl = 104, HCO3 = 24
glucose = 185, BUN = 20, Cr = 1.3
Hct = 36

Posm = 275, Uosm = 350, UNa+ = 60

O2 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?

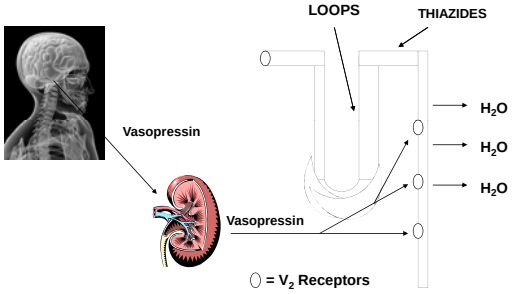
A. Yes
B. No

What do they do?

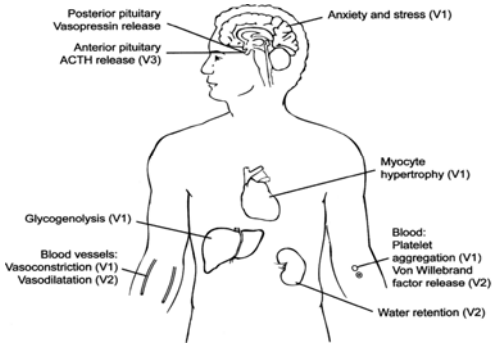
Diuresis:
increased excretion of urine by the kidney; includes water and typically increased solute excretion as well

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 ≥ 4mEq/L, time sodium ≥ 4mEq/L from baseline, # patients with ≥ 6mEq/L increase in sodium or normal (≥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.

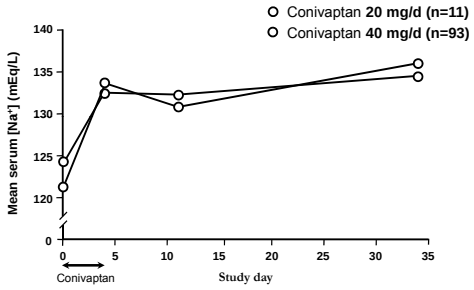
RESULTS

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 1st dose to Na ≥ 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 ≥ 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 Nephrology.* 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;11:6-13
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, indinivar

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
B. Vasodilation
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

Gheorghiade 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

<u>The Endpoints</u>

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
Gheorghiade 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, indinivar
- **Patients should be encouraged to drink when thirsty**
- **Co-administration with hypertonic saline: NR**

Tolvaptan [package insert]; 2009.

Tolvaptan Adverse Effects

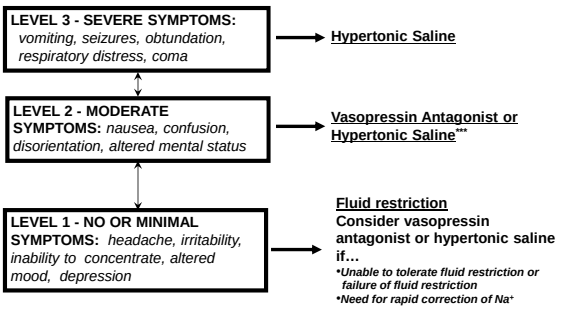
SALT studies

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

EVEREST

- Thirst
- Polyuria
- Pollakiuria
- Hypernatremia

HYPONATREMIA TREATMENT OPTIONS



***Vasopressin antagonists may be preferred if volume overloaded

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