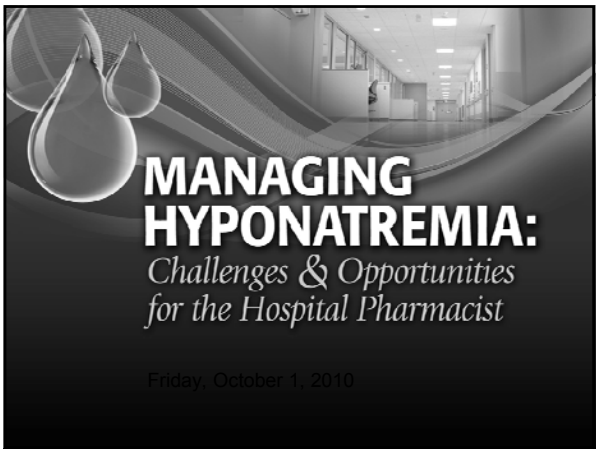
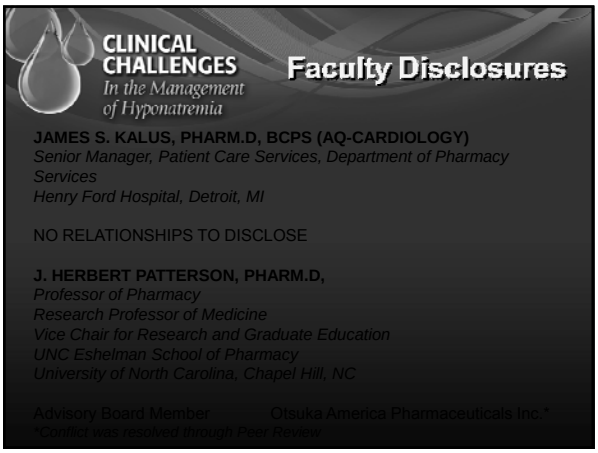



## Learning Objectives

- 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

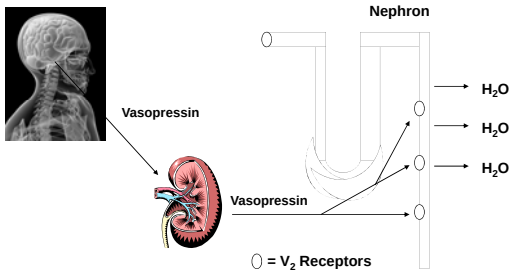
- **Most common electrolyte abnormality**
- **Associated with many systemic diseases**
  - Major: dilution of extracellular fluid
  - Minor: total body losses of sodium
- **Acute vs. Chronic**
  - Often duration is difficult to determine

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

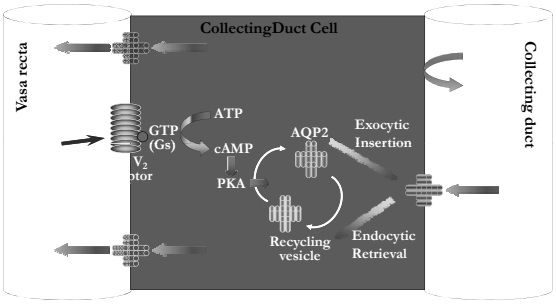
## Role of Vasopressin

- **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



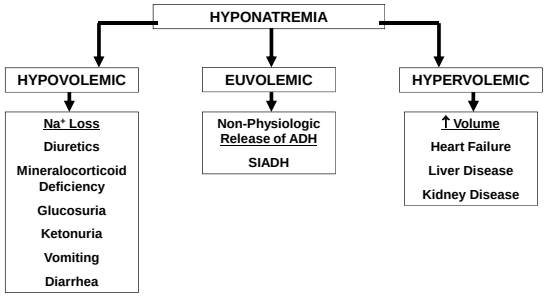

## AVP regulation of water reabsorption from renal tubular cells




## Classification: Osmolality

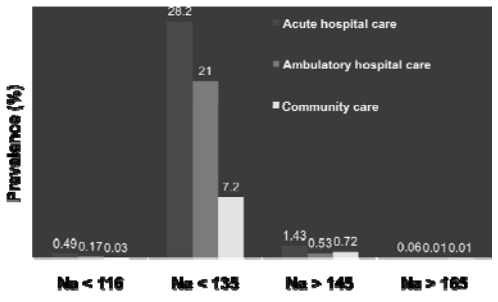
- **Hypotonic hyponatremia**
  - Sodium directly related to osmolality
  - Most cases
- **Isotonic/Hypertonic hyponatremia**
  - Pseudohyponatremia
  - Non-sodium solutes increase osmolality
    - Glucose
    - ↑ osmolality → fluid shifts → dilution of sodium

## 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%)**

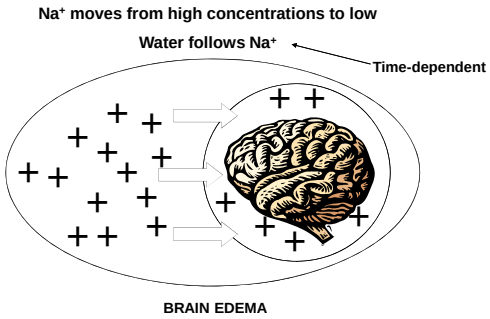
**223/223 resolved symptoms with correction of $[Na^+]$ via cessation of thiazide treatment**

## Increased Risk of Falls with "Asymptomatic" Hyponatremia

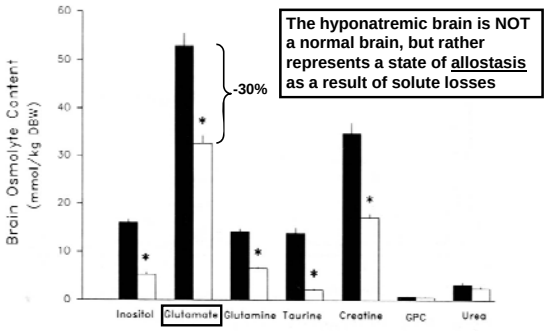
| Group | n | Falls | Odds Ratio | Adjusted Odds Ratio* |
|---|---|---|---|---|
| "Asymptomatic"Chronic Hyponatremia | 122 | 21.3% | 9.45 (2.64-34.09) p <.001 | 67.43 (7.48-607.42) p <.001 |
| Normonatremic controls | 244 | 5.35% | 1.00 | 1.00 |

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

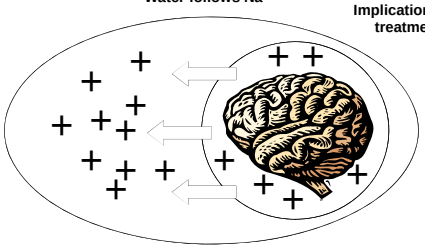
- **Acute hyponatremia**
  - Rapid onset
  - Greater likelihood of rapid fluid shifts and brain edema
- **Chronic hyponatremia**
  - Insidious onset
  - Less likelihood for brain edema
    - Time for compensatory increases in organic osmolytes

## 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.

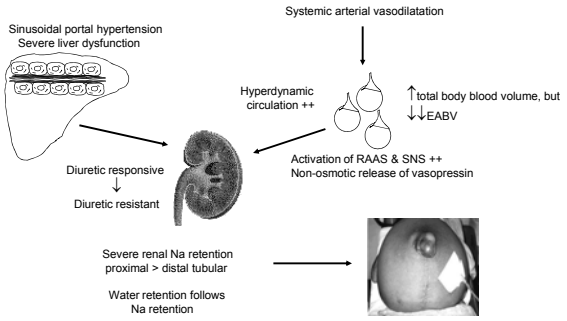
## Hyponatremia and Liver Disease

## Implications of Hyponatremia

**Liver Disease**

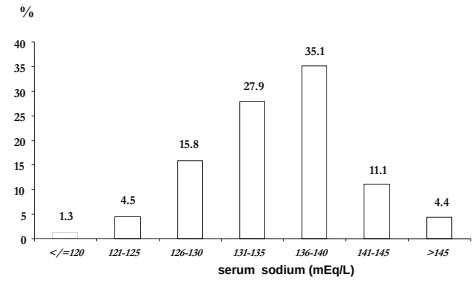
- Associated with poor prognosis & reduced survival
- Impairs the management of ascites
- Predisposes to hepatic encephalopathy
- Impairs quality of life

## 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.

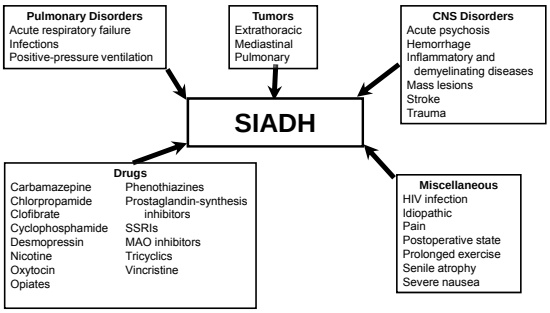
## Syndrome of inappropriate antidiuretic hormone (SIADH) secretion

## 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

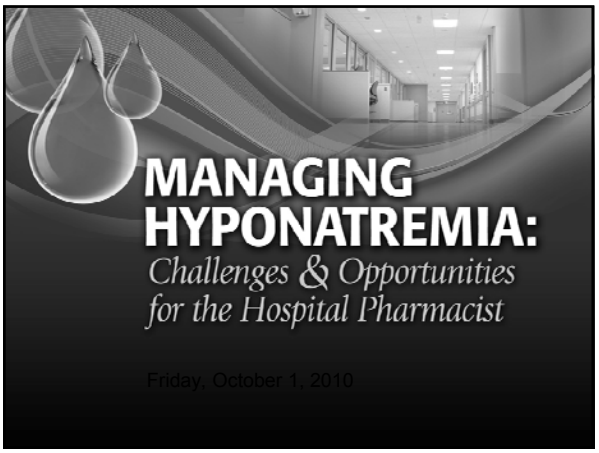
Bartter FC, et al. *Am J Med.* 1967; 42:790-806.

## 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

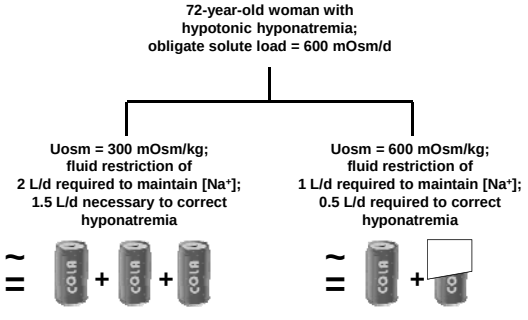
Which of the following medications is relatively contraindicated in the treatment of patients with cirrhosis because of a high incidence of nephrotoxicity?

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)<br>• Poorly tolerated due to thirst<br>• Should not be used with high AVP level and urine osmolality |
| Diuretics | • Allows relaxation of fluid restriction<br>• Potential for ototoxicity, volume depletion, and $K^+$ and $Mg^+$ depletion |
| Demeclocycline | • Not FDA approved for hyponatremia<br>• Slow to correct over days<br>• Nephrotoxic in cirrhosis and heart failure |
| Lithium | • Slow to correct<br>• Must monitor serum levels<br>• CNS side effects, cardiotoxic, GI disturbances |

## Urine Concentration Determines the Stringency of Water Restriction



## Current Treatment Strategies

| AGENT | LIMITATIONS |
|---|---|
| Isotonic saline | • Ineffective in dilutional hyponatremia<br>• Should not be used in setting of edema<br>• No safety data<br>• Complex calculations |
| Hypertonic saline | • No consensus regarding appropriate infusion rates<br>• Overcorrection can cause osmotic demyelination syndrome<br>• Should not be used in setting of edema<br>• No safety data<br>• 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?

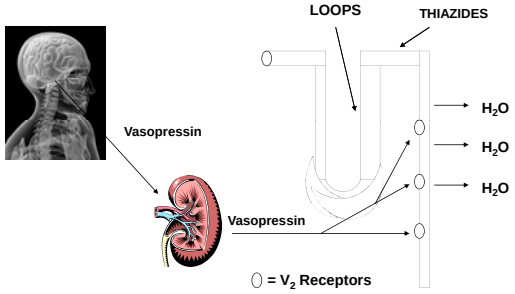
A. Yes
B. No

## What do they do?

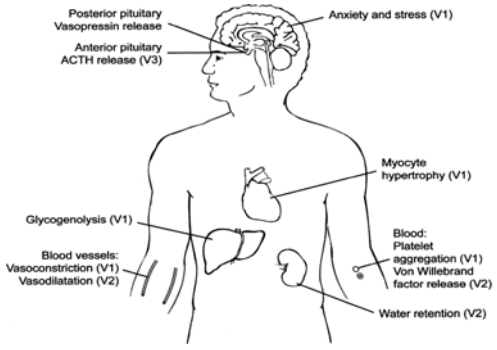
**Diuresis:**
increased excretion of urine by the kidney; includes water and typically increased solute excretion as well

**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<br>↑ 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.

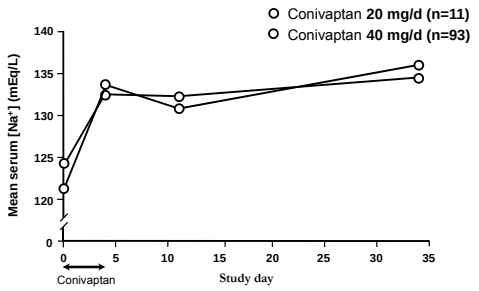
## RESULTS

| 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%<br>24h post D/C = 47% | No excessive correction<br>5 pts with phlebitis |
| #2 | 24 | Bolus only* | 72 hrs | Single Bolus: 56%<br>Double Bolus: 52% | 1 pt with excessive correction<br>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

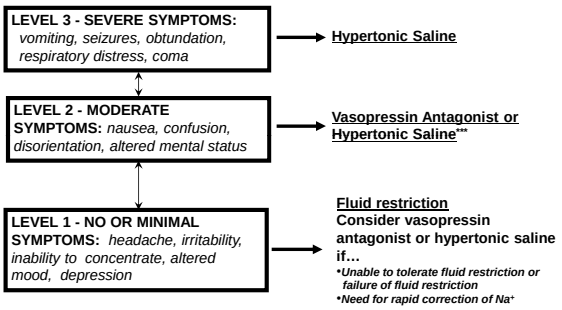
**SALT studies**

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

**EVEREST**

- Thirst
- Polyuria
- Pollakiuria
- Hypernatremia

## HYPONATREMIA TREATMENT OPTIONS




***Vasopressin antagonists may be preferred if volume overloaded

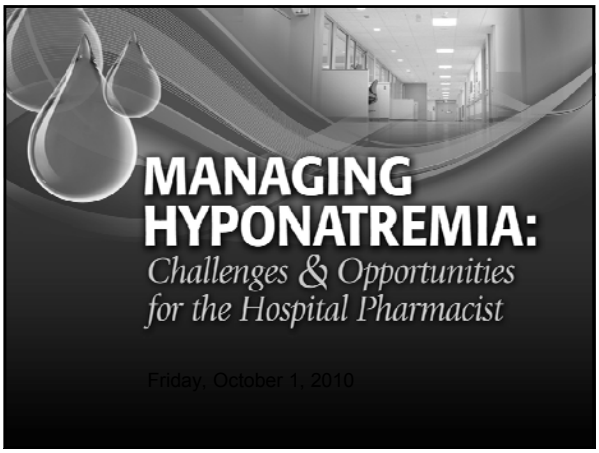
## Vasopressin Antagonist Formulary Considerations

- **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**


MANAGING
HYPONATREMIA:
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for the Hospital Pharmacist
Friday, October 1, 2010