Hyponatremia in Pituitary Patients

Lewis S. Blevins, Jr., M.D.

California Center for Pituitary Disorders at UCSF

Neurohypophysis

AVP secreting neurons in SON and PVN
Osmo- and thirst receptors/centers in anterior hypothalamus
Ascending pathways from ANS and brainstem
Terminal boutons in neurohypophysis

Relationship between Plasma Osmolarity and AVP

AVP Receptors

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Location</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>V1A</td>
<td>Vascular smooth muscle, platelets</td>
<td>Vasoconstriction, platelet aggregation</td>
</tr>
<tr>
<td>V1B</td>
<td>Anterior pituitary</td>
<td>ACTH release</td>
</tr>
<tr>
<td>V2</td>
<td>Renal collecting duct cells</td>
<td>Free water absorption</td>
</tr>
</tbody>
</table>

© Astellas
Aquaporins

Relationship between Urine Osmolarity and AVP

AVP Dynamics

Hyponatremia
one of many algorithms
Hyponatremia in Pituitary Patients

- Preoperative
  - Cortisol deficiency
  - Hypothyroidism
  - SIADH
    - rarely seen due to pituitary tumors
    - Not uncommon in hypothalamic tumors
- Immediate Postoperative
  - SIADH
- Delayed Postoperative
  - dDAVP excess
  - Other causes

Hyponatremia after Pituitary Surgery

- 32 of 1045 patients (3%) had preoperative hyponatremia
- 41% of these were symptomatic

- Postoperative hyponatremia after 165 operations (16%)
- Mean was 4 days after surgery with range of 0-28 days
- Preoperative hypopituitarism was the only independent predictor of a likelihood to develop hyponatremia
Hyponatremia

- Disorders or processes that cause hyponatremia are dynamic:
  - Initiation
  - Maintenance
  - Recovery
- It is critical to ascertain where the patient might be in their course as one initiates and measures a response to management.

Hyponatremia Symptoms and Signs

<table>
<thead>
<tr>
<th>Feature</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea/Vomiting</td>
<td>71</td>
</tr>
<tr>
<td>Delerium/Confusion</td>
<td>50</td>
</tr>
<tr>
<td>Weakness</td>
<td>50</td>
</tr>
<tr>
<td>Lethargy</td>
<td>50</td>
</tr>
<tr>
<td>Myalgia/Cramps</td>
<td>21</td>
</tr>
<tr>
<td>Dizziness</td>
<td>21</td>
</tr>
<tr>
<td>Hiccups</td>
<td>14</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>14</td>
</tr>
</tbody>
</table>


Severe Hyponatremia
168 patients Na+ <115 mEq/L

Symptoms of Hyponatremic Encephalopathy

Altered Sensorium
Seizures
Nausea & Vomiting
Gait disturbance & Falls
Dysarthria
Coma


Hyponatremia

Hyponatremia

Outcomes of Correction

Osmotic Demyelination

Central Pontine Myelinolysis
Central Demyelination Syndrome

Central Demyelination

- Demyelination injury to oligodendrocytes
- Disruption of blood brain barrier may play a role
- Accumulation of microglial cells
- Release of pro-inflammatory cytokines
- Destruction of myelin
- Animal studies suggest minocycline and lovastatin may be protective

Clinical Features of Osmotic Demyelination

<table>
<thead>
<tr>
<th>Feature</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutism/Dysarthria</td>
<td>71</td>
</tr>
<tr>
<td>Lethargy/Obtundation</td>
<td>57</td>
</tr>
<tr>
<td>Behavioral changes</td>
<td>29</td>
</tr>
<tr>
<td>Confusion</td>
<td>21</td>
</tr>
<tr>
<td>Movement difficulty</td>
<td>21</td>
</tr>
<tr>
<td>Muscle contractions</td>
<td>7</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical Features of Osmotic Demyelination</th>
<th></th>
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<tbody>
<tr>
<td>Spasticity, rigidity, Babinski reflex, hyperreflexia, impaired gag reflex, fasciculations, nonreactive or dilated pupils, snout, grasp or rooting reflexes, impaired gait, ataxia, cognitive deficits.</td>
<td></td>
</tr>
</tbody>
</table>
Reducing risks of myelinolysis

- Limit correction of chronic hyponatremia to 10 to 12 mmol/L in 24 hours and to 18 mmol/L in 48 hours.
- When other recognized risk factors for myelinolysis are present (menstruant women, hypokalemia, liver disease, poor nutritional state, alcoholism, burns), correction should not exceed 10 mEq/L/24h.
- In acute hyponatremia a more rapid initial correction rate, roughly 1-2 mEq/L, is acceptable.

Hyponatremia
Common Sense

- Acute treatment should be interrupted once any of 3 end points is reached:
  - the patient’s symptoms are abolished;
  - a safe serum [Na] level (>120 mEq/L) is achieved;
  - a total magnitude of correction of 18 mEq/L is achieved.

Judicious use of 3% Saline

- Hyponatremic patients with significant neurological symptoms, such as seizures, severe altered mental status, or coma
- The high likelihood of cerebral edema outweighs the risk of possible demyelination.
- Target rate of correction is 1.5 to 2 mEq/L per hour with 3% hypertonic saline for the first 3 to 4 hours, or more briefly, if symptoms improve or the sodium level exceeds 120 mEq/L.

3% Saline
An Alternative Approach

- Rate in mL/h is the desired rate of rise in Na+ in mEq/L/h per kg body weight
- Furosemide 20 mg iv
- For a 70 kg patient with desired correction rate of 1.5 mEq/L 3% saline infusion rate would be 105 mL/h.
Fluid restriction

? 

Vasopressin Receptor Antagonists

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Receptor</th>
<th>Effective Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conivaptan</td>
<td>IV/Oral</td>
<td>V1/V2</td>
<td>20-40 mg/d</td>
</tr>
<tr>
<td>Tolvaptan</td>
<td>Oral</td>
<td>V2</td>
<td>15-60 mg/d</td>
</tr>
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</table>


Use of Intravenous Conivaptan in Neurosurgical Patients With Hyponatremia From Syndrome of Inappropriate Antidiuretic Hormone Secretion

Matthew B. Pettis, MD*
Anthony F. DeGiacomo, MD*
Leona Dargazany, PharmD*
Lewis S. Sback, Jr, MD*

*Department of Neurological Surgery and *California Center for Phlebitis Disorders, University of California, San Francisco, San Francisco, California

Conivaptan:
Matthew B. Pettis, MD
351 University Ave
M7, UCSF Box 0012
San Francisco, CA 94143-0012
E-mail: pettism@neurosurgery.ucsf.edu

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BACKGROUND: Syndrome of inappropriate antidiuretic hormone secretion (SIADH) is the most common cause of hyponatremia in hospitalized patients and is frequently associated with neurologic disorders and neurosurgical procedures. Traditional therapies such as fluid restriction, sodium repletion, and diuretics can help correct hyponatremia but do not address the underlying pathophysiology of excess arginine vasopressin secretion. Conivaptan is an arginine vasopressin receptor antagonist that has been shown to be both safe and effective in the treatment of euvolemic and hypervolemic hyponatremia.

OBJECTIVE: To analyze the use of conivaptan to treat SIADH in a mixed neurosurgical population.

METHODS: We conducted a retrospective review of 13 patients with neurosurgical disorders with SIADH that were treated with intravenous conivaptan at our institution between 2007 and 2009.

RESULTS: The mean pretreatment serum sodium concentration was 125.8 ± 3.5 mEq/L. Conivaptan administration resulted in a rise in serum sodium to 132.5 ± 5.6 mEq/L at 12 hours (P < .01) and 134.1 ± 4.7 mEq/L at 24 hours posttreatment (P < .01). The mean time to an increase in serum sodium ≥ 6 mEq/L was 17.8 hours. There were no instances of rapid counter-regulation. There were 1 cases of asymptomatic hypokalemia, 1 case of asymptomatic hyperkalemia, and 1 case of elevated creatinine associated with conivaptan administration.

CONCLUSIONS: These data provide further support that conivaptan can be safely used for the treatment of SIADH-induced hyponatremia in the neurosurgical arena.

KEY WORDS: Antidiuretic hormone, Arginine vasopressin, Conivaptan, Hyponatremia, SIADH, Vasopressin

Vaprisol at UCSF

- Na+ 125 mEq/L at baseline
- Na+ 134 mEq/L at 24h
- 5 patients required a second dose
- 2 patients required more than 2 doses
- I/O 1.4L negative first day of Rx
- Eight patient had sellar lesions and 6 were post TSA
  - Sodium levels 124 → 132 → 134 mEq/L at baseline, 12h and 24h
  - 6 mEq/L achieved in 10 hrs
  - No recurrent hyponatremia
Conivaptan IV

8-10% experience rapid correction


Conivaptan IV

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Tolvaptan in the Management of Hyponatremia

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Hyponatremia after Pituitary Surgery

- Mean correction rates (mEq/L)
  - No Treatment: 0.4
  - Fluid restriction: 0.5
  - Salt tablets: 0.7
  - 3% saline: 0.3
  - Vaprisol: 0.7
  - Tolvaptan: 1.2

Hyponatremia due to dDAVP excess

- Prevention is essential
- Check labs!!!
- Must control rate of rise of sodium
- Small dose of AVP or dDAVP often administered as soon as aquareesis begins due to waning drug effect
- Be quick to lift fluid restriction!!!!

Water is a marvelous life sustaining and yet simple molecule that must be offered tremendous respect for it can be a very dangerous thing in many different ways.