Biruh Tesfa Workeneh, MD, FASN

- University of Texas McGovern Medical School
- Medicine Residency University of Texas Medical Branch
- Stanford University Nephrology Fellowship
- Professor of Medicine
- University of Texas MD Anderson Cancer Center
  - Dialysis Medical Director
  - Clinical and research interests: Onconephrology Education, Optimizing Hyponatremia Management in Cancer Patients
Treatment of Hyponatremia in Cancer Patients:
The Role of Vaptans and Urea

Biruh Tesfa Workeneh, MD, FASN
Professor of Medicine
Section of Nephrology
MD Anderson Cancer Center
Disclosures

• I have the following financial disclosures

• Consultant: Otsuka, AstraZeneca
Objectives

- Articulate rationale for treating hyponatremia in cancer patients
- Describe the mechanism of action of urea and vaptans, and clinical data to support its use
- Contrast urea and vaptan therapy with alternative interventions in cancer patients and also understand its limitations
- Be able to make informed decisions about use of urea and vaptans in clinical practice
Why is hyponatremia so common in cancer patients?

**Table 1. Causes of syndrome of inappropriate antidiuresis**

<table>
<thead>
<tr>
<th>Tumors</th>
<th>Infections</th>
<th>Drugs</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extrapulmonary small cell carcinoma</td>
<td>AIDS</td>
<td>Chemotherapy agents</td>
<td>Postoperative state (major)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>Encephalitis</td>
<td>Cyclophosphamide</td>
<td>abdominal or thoracic surgery;</td>
</tr>
<tr>
<td>Meningeal carcinomatosis</td>
<td>Hydrocephalus</td>
<td>Ifosfamide</td>
<td>pituitary surgery or other</td>
</tr>
<tr>
<td>Metastatic brain and spine tumors</td>
<td>Idiopathic, particularly in the elderly</td>
<td>Vinristine</td>
<td>neurosurgery</td>
</tr>
<tr>
<td>Olfactory neuroblastoma</td>
<td>Meningitis</td>
<td>Vinblastine</td>
<td>Hydrocephalus</td>
</tr>
<tr>
<td>Ovarian teratoma</td>
<td>Pneumonia (bacterial and viral)</td>
<td>Melphanal</td>
<td>Cavernous sinus Thrombosis</td>
</tr>
<tr>
<td>Endometrial carcinoma</td>
<td>Pulmonary abscess</td>
<td>Methotrexate</td>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>Pancreatic carcinoma</td>
<td>Aspergillosis</td>
<td>Targeted Therapies:</td>
<td>Guillain-Barre Syndrome</td>
</tr>
<tr>
<td>Primary brain tumors</td>
<td>Tuberculosis</td>
<td>Afatinib</td>
<td>Delirium Tremens</td>
</tr>
<tr>
<td>Prostate carcinoma</td>
<td>Brain abscess</td>
<td>Brivanib</td>
<td>Acute intermittent porphyria</td>
</tr>
<tr>
<td>Bladder carcinoma</td>
<td>Rocky mountaini spotted fever</td>
<td>Cetuximab</td>
<td>Acute respiratory failure</td>
</tr>
<tr>
<td>Small cell lung carcinoma and other pulmonary tumors</td>
<td></td>
<td>Gefitinib</td>
<td>Acute Psychosis</td>
</tr>
<tr>
<td>Thymic tumors</td>
<td>Malaria</td>
<td>Linifanib</td>
<td>Stroke</td>
</tr>
<tr>
<td>Sarcomas</td>
<td></td>
<td>Pazopanib</td>
<td>Subarachnoid hemorrhage and other intracranial hemorrhages</td>
</tr>
</tbody>
</table>

Non-chemotherapy agents
Desmopressin/Vasopressin
Methyleneedoxymethamphetamine
NSAIDs
Opiates
Oxytocin
Phenothiazines
Prostaglandin-synthesis inhibitors
Rosiglitazone
Selective serotonin reuptake inhibitors (SSRIs)
Selective norepinephrine reuptake inhibitors (SNRIs)
Thiazide diuretics
Ciprofloxacin
Tricyclic antidepressants
Chloropramide

Why is hyponatremia so common in cancer patients?

<table>
<thead>
<tr>
<th>Tumors</th>
<th>Infections</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extrapulmonary small cell carcinoma</td>
<td>AIDS</td>
<td>Chemotherapy agents</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>Encephalitis</td>
<td>Cisplatin</td>
</tr>
<tr>
<td>Meningeal carcinomatosis</td>
<td>Hydrocephalus</td>
<td>Cyclophosphamide</td>
</tr>
<tr>
<td>Metastatic brain and spine tumors</td>
<td>Idiopathic, particularly in the elderly</td>
<td>Ifosfamide</td>
</tr>
<tr>
<td>Olfactory neuroblastoma</td>
<td>Meningitis</td>
<td>Vinristine</td>
</tr>
<tr>
<td>Ovarian teratoma</td>
<td>Pneumonia (bacterial and viral)</td>
<td>Vinblastine</td>
</tr>
<tr>
<td>Endometrial carcinoma</td>
<td></td>
<td>Melphalan</td>
</tr>
<tr>
<td>Pancreatic carcinoma</td>
<td>Pulmonary abscess</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>Primary brain tumors</td>
<td>Aspergillosis</td>
<td>Targeted Therapies:</td>
</tr>
<tr>
<td>Prostate carcinoma</td>
<td>Tuberculosis</td>
<td>Afatinib</td>
</tr>
<tr>
<td>Bladder carcinoma</td>
<td>Brain abscess</td>
<td>Brivanib</td>
</tr>
<tr>
<td>Small cell lung carcinoma and other pulmonary tumors</td>
<td>Rocky mountain spotted fever</td>
<td>Cetuximab</td>
</tr>
<tr>
<td>Thymic tumors</td>
<td></td>
<td>Geftinib</td>
</tr>
<tr>
<td>Sarcomas</td>
<td></td>
<td>Linifanib</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pazopanib</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sorafenib</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vorinostat</td>
</tr>
</tbody>
</table>

Targeted Therapies:

- Afatinib
- Brivanib
- Cetuximab
- Geftinib
- Linifanib
- Pazopanib
- Sorafenib
- Vorinostat

Consequences of Hyponatremia

The most common clinical manifestations at diagnosis of hyponatremia were unsteadiness with falls (52.8%), confusion and mental slowing (38.9%), asthenia (25%), headache (22.2%), nausea and vomiting (11.1%).
Adaptive response to hyponatremia

- Mild chronic hyponatremia is defined as $\text{SNa} > 72$ hours between $125$ and $135$ mEq/L without apparent symptoms.
- Threshold $[\text{Na}]$ at which deficits consistently appear is $132$ mEq/L.
- Cerebral loss of osmolytes including neurotransmitters (e.g., glutamate); induces neurocognitive effects.

Adrogue/Madias, NEJM 2000.
Neurocognitive deficits present in mild hyponatremia

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Study</th>
<th>Cohort Size</th>
<th>Mean PNa ± SD (mEq/L)</th>
<th>Neurocognitive Assessment Tool</th>
<th>Outcomes of Hyponatremia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renneboog et al. (18)</td>
<td>Crossover</td>
<td>16</td>
<td>128±3</td>
<td>Battery of attention tests(^b)</td>
<td>Median latencies increased by 58 ms ((P&lt;0.001)) and no. of errors increased 1.2-fold ((P=0.001))</td>
</tr>
<tr>
<td>Gosch et al. (19)</td>
<td>Retrospective case control</td>
<td>258</td>
<td>128±3.2</td>
<td>MMSE and CC</td>
<td>In multivariate analyses, hyponatremia was a significant predictor for abnormal scores on the MMSE ((P=0.04); OR, 1.96; 95% CI, 1.05 to 3.68) and CC ((P=0.02); OR, 2.57; 95% CI, 1.19 to 5.55)</td>
</tr>
<tr>
<td>Gunathilake et al. (20)</td>
<td>Prospective cohort</td>
<td>2550</td>
<td>135 versus 130(^a)</td>
<td>ARCS</td>
<td>Scores were, on average, 4.67 units significantly lower ((P=0.01))</td>
</tr>
</tbody>
</table>

PNa, plasma sodium concentration; MMSE, Mini-Mental State Examination; CC, Clock Completion test; ARCS, Audio Recording Cognitive Screening tool; OR, odds ratio; 95% CI, 95% confidence interval.

\(^a\)Study compared patients with PNa of 135 versus 130 mEq/L. No mean PNa was provided.

\(^b\)Visual Vigilance, Working Memory or Digit Span, Go/No Go, Intermodal Comparison, Divided Attention, and Phasic Alert.
Neurocognitive deficits present in mild hyponatremia

<table>
<thead>
<tr>
<th>PNa ±SD (mEq/L)</th>
<th>Neurocognitive Assessment Tool</th>
<th>Outcomes of Hyponatremia</th>
</tr>
</thead>
<tbody>
<tr>
<td>128±3</td>
<td>Battery of attention tests(^b)</td>
<td>Median latencies increased by 58 ms ((P&lt;0.001)) and no. of errors increased 1.2-fold ((P=0.001))</td>
</tr>
<tr>
<td>128±3.2</td>
<td>MMSE and CC</td>
<td>In multivariate analyses, hyponatremia was a significant predictor for abnormal scores on the MMSE ((P=0.04); OR, 1.96; 95% CI, 1.05 to 3.68) and CC ((P=0.02); OR, 2.57; 95% CI, 1.19 to 5.55)</td>
</tr>
<tr>
<td>versus 130(^a)</td>
<td>ARCS</td>
<td>Scores were, on average, 4.67 units significantly lower ((P=0.01))</td>
</tr>
</tbody>
</table>

PNa, plasma sodium concentration; MMSE, Mini-Mental State Examination; CC, Clock Completion test; ARCS, Audio Recording Cognitive Screening tool; OR, odds ratio; 95% CI, 95% confidence interval.

\(^a\)Study compared patients with PNa of 135 versus 130 mEq/L. No mean PNa was provided.

\(^b\)Visual Vigilance, Working Memory or Digit Span, Go/No Go, Intermodal Comparison, Divided Attention, and Phasic Alert.

Rondon/Berl. CJASN, 2015.
Hyponatremia increases Fall Risk

The recorded projection of the center of gravity over a pressure-sensitive calibrated platform (10 sec tandem walk) in patients before after hyponatremia correction.
Hyponatremia increases Fall Risk

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Study</th>
<th>Cohort Size</th>
<th>Mean PNa ±SD (mEq/L)</th>
<th>Fall Risk (OR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renneboog et al. (18)</td>
<td>Cross-sectional</td>
<td>366</td>
<td>126±5</td>
<td>67.43 (95% CI, 7.5 to 607)</td>
</tr>
<tr>
<td>Bun et al. (21)</td>
<td>Retrospective case control</td>
<td>248</td>
<td>131.82±2.99</td>
<td>4.38 (95% CI, 1.33 to 14.46)</td>
</tr>
<tr>
<td>Gunathilake et al. (20)</td>
<td>Prospective cohort</td>
<td>2550</td>
<td>135 versus 130</td>
<td>1.32 (95% CI, 1.04 to 1.64)</td>
</tr>
</tbody>
</table>

PNa, plasma sodium concentration; OR, odds ratio; 95% CI, 95% confidence interval.

aStudy compared patients with PNa of 135 versus 130 mEq/L. No mean PNa was provided.
Hyponatremia is significant risk factor for Fracture

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Study</th>
<th>Cohort Size</th>
<th>Definition of Hyponatremia (mEq/L)</th>
<th>Mean PNa ± SD (mEq/L)</th>
<th>All Fracture Risk (OR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gankam Kengne et al. (22)</td>
<td>Retrospective case control</td>
<td>1026</td>
<td>&lt;134</td>
<td>131±3</td>
<td>4.16 (95% CI, 2.2 to 47.71)</td>
</tr>
<tr>
<td>Sandhu et al. (23)</td>
<td>Retrospective case control</td>
<td>728</td>
<td>&lt;135</td>
<td>131±2</td>
<td>2.34 (95% CI, 1.24 to 4.35)</td>
</tr>
<tr>
<td>Kinsella et al. (24)</td>
<td>Retrospective case control</td>
<td>1408</td>
<td>&lt;135</td>
<td>132.2±1.8</td>
<td>2.25 (95% CI, 1.24 to 4.09)</td>
</tr>
<tr>
<td>Hoorn et al. (11)</td>
<td>Prospective cohort</td>
<td>5208</td>
<td>&lt;136</td>
<td>133.4±2</td>
<td>1.34b (95% CI, 1.08 to 1.68)</td>
</tr>
<tr>
<td>Tolouian et al. (25)</td>
<td>Retrospective case control</td>
<td>293</td>
<td>&lt;136</td>
<td>a</td>
<td>4.8c (95% CI, 1.06 to 21.67)</td>
</tr>
<tr>
<td>Jamal et al. (26)</td>
<td>Prospective cohort</td>
<td>5122</td>
<td>&lt;135</td>
<td>132.3±1.8</td>
<td>3.48d (95% CI, 1.76 to 6.87)</td>
</tr>
</tbody>
</table>

PNa, plasma sodium concentration; OR, odds ratio; 95% CI, 95% confidence interval.

*a* Mean PNa not provided in the publication.

*b* Hazard ratio for nonvertebral fractures.

*c* OR for hip fracture.

*d* Hazard ratio for hip fracture.
Osteoporosis


Hyponatremia was associated with reduced overall survival
Hyponatremia was associated with reduced overall survival

Fuca et al. Sci Rep, 2019
Hyponatremia outcomes

Hyponatremia Intervention Trial (HIT): Study Protocol of a Randomized, Controlled, Parallel-Group Trial With Blinded Outcome Assessment

Julie Refardt\textsuperscript{1,2,3,*}, Anissa Pelouto\textsuperscript{4,*}, Laura Potasso\textsuperscript{1,2,3,*}, Ewout J. Hoorn\textsuperscript{4} and Mirjam Christ-Crain\textsuperscript{1,2,3,*} on behalf of the HIT study group

\textsuperscript{1} Departments of Endocrinology, Diabetology and Metabolism University Hospital Basel, Basel, Switzerland
\textsuperscript{2} Department of Clinical Research, University of Basel, Basel, Switzerland
\textsuperscript{3} Clinical Trial Unit, Department of Clinical Research, University of Basel and University Hospital Basel, Basel, Switzerland
\textsuperscript{4} Department of Internal Medicine, Division of Nephrology and Transplantation, Erasmus MC, University Medical Center Rotterdam, Rotterdam, Netherlands

Fuca et al. Sci Rep, 2019
Case

History: 52 yo man (Charlie) with a recent diagnosis of SCLC, admitted from after found to have a SNa of 119mmol/L in clinic; does not provide h/o nausea, vomiting, diarrhea and not on diuretics and has not started chemotherapy. You are consulted for evaluation and management of hyponatremia

Physical exam
BP 130/80 HR 80 RR 12 T Afebrile
Alert and oriented
Regular heart rhythm
No peripheral edema
No focal neurologic deficits
Labs

- Na = 119mmol/L
- BUN = 10mg/dL
- SCr = 0.8mg/dL
- Sosm = 265 mOsm/kg
- Uric acid = 2.0mg/dL
- TSH 1.8mU/L
- Cortisol = 20mcg/dL

- UNa = 80mEq/L
- UK = 50mEq/L
- Uosm = 500mOsm/kg
What are our options?

- Fluid restriction
- Loop diuretic + salt tabs
- Vasopressin receptor-2 blocker
- Salt tablets
- Urea
 Patients with SIADH has negative electrolyte free water clearance and therefore have tendency to retain water

A short-cut for the above equation is:

\[
\frac{\text{(UNa + UK)}}{\text{PNa}}
\]

>1 means unlikely to improve even with very restrictive measures; also if Uosm >500mOsm/L; try another other strategy

May be good idea to treat xerostomia (biotene, neutrasal, cevilamine, etc.)

This approach takes several days to correct sNa

<table>
<thead>
<tr>
<th>(UNa+UK)/PNa</th>
<th>Insensible Water Losses (ml)</th>
<th>Water Loss beyond Insensible Losses (ml)</th>
<th>Recommended Fluid Restriction (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1</td>
<td>800</td>
<td>0–800*</td>
<td>0</td>
</tr>
<tr>
<td>0.5–1</td>
<td>800</td>
<td>300–800</td>
<td>≤500</td>
</tr>
<tr>
<td>&lt;0.5</td>
<td>800</td>
<td>300–800</td>
<td>≤1000</td>
</tr>
</tbody>
</table>

Normal “idealized” physiology

600mOsm

2L

Solute balance: 0

Urine Osm: 300mOsm/L

Water balance: 0

600mOsm
SIADH

Solute balance: 0

Urine Osm: 500mOsm/L (Fixed)

Water balance: +0.8L
Salt tabs

600mOsm + 200mOsm

2L

2L

800mOsm

Urine Osm: 500mOsm/L (Fixed)

Water balance: +0.4L

Solute balance: 0

Rx: Salt tabs 2 grams TID

6g converted to mOsm = ~200mOsm
Loop diuretics

- Solute balance: 0/-
- Water balance: -2L

600mOsm

2L

600mOsm

2L 4L

Urine Osm: 150mOsm/L
Lasix effect

Water balance: -2L
**Urea**

600mOsm + 500mOsm → 1100mOsm

2L → 2.2L

Solute balance: 0

Urine Osm: 500mOsm/L (Fixed)

Water balance: -0.2L

Rx: Urea 15g bid

30g urea (MW 60) = 500mOsm

Mechanism: Induces osmotic diuresis; Decreases the compensatory natriuresis in SIADH
Mechanism of Action

Induces osmotic diuresis and electrolyte-free water loss
Urea origins: "Gold of the blood"

- Urine therapy has been used for centuries; it has been swallowed, gargled, placed on ulcers/wounds for its various “medicinal effects”
- Oral urea first used as a diuretic in 1892, throughout the 1900s in advanced heart failure
- Intravenous urea used for the treatment of elevated intracranial and intraocular pressure (given the osmotic properties of urea), but its use faded with the introduction of mannitol; last formulation of IV urea was discontinued in 2006
- Decaux and colleagues reported first use of oral urea to treat hyponatremia in the modern era in 1980s and have published several additional articles demonstrating its efficacy

Modern formulations

- Bitter taste; flavored versions
- Small amount undergoes hydrolysis in the colon producing ammonium

\[
2 \text{NH}_3 + \text{CO}_2 \rightleftharpoons \text{H}_2\text{N} - \text{COONH}_4 \quad \text{(Carbamate formation)}
\]

\[
\text{H}_2\text{N} - \text{COONH}_4 \rightleftharpoons (\text{NH}_2)_2\text{CO} + \text{H}_2\text{O} \quad \text{(Urea conversion)}
\]

Lessons learned (evolution of practice)

  • SNa 115mmol/L (+/-6.5) > 135mmol/L (+/-3.5)
  • 4/7 total patients had inoperable small cell lung cancer
  • Patients treated for up to 270 days (long term tolerability)

• Decaux et al. Critical Care 2010 (85 pts total, retrospective cohort)
  • Included patients with G-tube; cancer demographics not given
  • Urea improved both moderate hyponatremia 120-134mmol/L and severe hyponatremia <115mmol/L

• Lockett et al. Clin Endocrinol, 2019
  • 10/78 patients with malignancy (7 with SCLC)
  • Mean SNa 122; 64% achieved SNa >130mmol/L

• Handful of studies including SIADH from various causes, also using urea for other indications (CHF, cirrhosis, primary polydipsia)
Clinical Efficacy

• There are limited clinical trials in cancer patients focused on the treatment of hyponatremia in cancer patients; thus, experience in other settings is extrapolated

• Dosing recommendations for SIADH (Decaux):
  • UOsm ≈ 300: Urea 15 g PO daily
  • UOsm ≈ 500-600: Urea 15 g PO BID and fluid restriction 1.5-2 L/day
  • Able to relax fluid restriction
Nervo et al. Clin Endocrinol, 2019

- Retrospective analysis of 36 cancer patients with SIADH
- Started oral urea (initial daily dose 15 g or 30 g) without fluid restriction between July 2013 and July 2018
- Analyzed SNa increase after 24 hours; and % of patients achieving eunatremia within 14, 30 and 60 days

**TABLE 1** Distribution of patients according to tumour type

<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung cancer</td>
<td>21</td>
</tr>
<tr>
<td>Gastrointestinal neuroendocrine tumour</td>
<td>4</td>
</tr>
<tr>
<td>Head and neck cancer</td>
<td>3</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>3</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>1</td>
</tr>
<tr>
<td>Chronic lymphocytic leukaemia</td>
<td>1</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>1</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>1</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>36</td>
</tr>
</tbody>
</table>
Clinical outcomes

- **SNa rise (mmol/L) after 24 h of therapy**
  - Percentage of patients
  - 0-2: 10%
  - 3-4: 30%
  - 5-6: 20%
  - 7-8: 10%
  - 9-10: 5%
  - 11-12: 5%

- **Percentage of eunatremic patients**
  - Within 14 d: Moderate hyponatremia (at diagnosis): 60%
  - Within 30 d: Profound hyponatremia (at diagnosis): 80%
  - Within 60 d: Profound hyponatremia (at diagnosis): 100%
- 13 patients with chronic SIADH from varying causes
- 1 withdrew due to excessive thirst/hypernatremia receiving vaptan (satavaptan or tolvaptan)
- 1 patient admitted for hypernatremia receiving urea

Soupart 2012
V2 receptor blocker for SIADH

• Label is for initiation in hospital setting in cases of hyponatremia
• Ad libitum diet
• Caution for over-correction
• Long-term liver toxicity surveillance

Vaptans: clinical evidence in cancer

• SALT-1 and SALT-2 were phase 3, multicenter, double-blind, placebo-controlled trials assessing the efficacy and safety of tolvaptan in subjects with euvolemic or hypervolemic hyponatremia

• Post hoc subgroup analysis of the SALT trials

Gralla et al. Cancer Med. 2017

Table 1
Demographics and baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Tolvaptan</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>Age, mean years ± SD</td>
<td>63 ± 12</td>
<td>65 ± 10</td>
</tr>
<tr>
<td>Male, %</td>
<td>33.3</td>
<td>62.5</td>
</tr>
<tr>
<td>Caucasian, %</td>
<td>75.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Baseline serum sodium, mean mEq/L ± SD</td>
<td>130 ± 2.9</td>
<td>128 ± 5.2</td>
</tr>
<tr>
<td>Tumor types, n</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Head and neck</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Breast</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Renal</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Ovarian</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Gall bladder</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Skin</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Uterine</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Prostate</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Adenocarcinoma of the</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>
Equally effective in cancer vs other causes of SIADH

- High cost continues to be a limitation for routine use
- Overcorrection and ODS can occur
- AEs were similar to the general SIADH group
- Caution for liver toxicity

No patient exhibited overly rapid correction of serum sodium, defined as >8 mEq/L change by first 8 h or >12 mEq/L change by the first 24 h
High sensitivity to tolvaptan in paraneoplastic syndrome of inappropriate ADH secretion (SIADH)

- Consider lower dose of tolvaptan 7.5mg or even lower (3.75mg)
- Limited data with Q48h or Q72h also show effectiveness

Ren et al. Transl Cancer Res. 2021
Specter of Osmotic demyelination syndrome

- The risk of ODS after hyponatremia is corrected within the recommended range regardless of the drug used is extremely low, but given **devastating** consequences, wise to monitor and mitigate

- Overcorrection of hyponatremia > 12mmol/L in 6h induces severe neurological manifestations and demyelination with HTS and V2R antagonist; the exception was urea

- Animal studies provide only hypothesis generation and caution should be used with **any** agent used to increase SNa concentration

Clinic addressing low sodium levels opening Oct. 6

Thursday, September 28, 2017

If you're concerned that a patient may be suffering from low sodium levels, you can now refer them to our Hyponatremia Clinic, opening on Fridays beginning Oct. 6.

Hyponatremia is the most common electrolyte disorder seen in cancer patients, and it can lead to other health concerns if not treated. Many treatments and comorbidities can cause low sodium levels, and it's important to address quickly.

What to look for

Hyponatremia is most often seen in patients with small cell cancer, though it can be present in any patient. Mild symptoms can lead to attention deficits and unsteadiness gait, which can cause falls and more serious conditions.

Mild symptoms of hyponatremia include:

- Headaches
- Nausea
- Hiccups

Patients should get a referral to the Hyponatremia Clinic if their sodium level is less than 133.

More severe symptoms (lethargy, confusion, seizures, and coma) should go directly to the Emergency Center.

Make a referral
Urea: Take Home Messages

1. Urea is considered a medical food; works as an osmotic diuretic
2. Urea is effective in treating hyponatremia and performs similarly to other therapies
3. Urea has a good safety profile, but patients with GI cancers, or nausea/vomiting may not tolerate
4. Overcorrection CAN occur with urea therapy; caution should be taken with any therapy for hyponatremia
Vaptans: Take Home Messages

1. Oral vaptans work on V2R blocking action of ADH
2. Only therapy for SIADH that has RCT data, although most patients studied were without cancer
3. Global health care costs for treating SIADH is higher; may be challenging in low resourced settings
4. ODS has been reported and there may be sensitivity to the drug in Cancer/SIADH, consider using a modified lower dose, at least to start
Thank You

Any Questions?