Hyponatraemia / SIADH

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Supportive Care in Cancer, RCP 5th November 2015
First, let's put this in context...
Oct 2013 (67yr F).

Known COPD
Admitted with infective exacerbation
Nodule noted at right hilum
Staging CT & transbronchial biopsy
Dx: Small cell lung
  S.Na⁺ 124 mmol/l

MDT:  Not amenable to surgery
  For chemotherapy (carboplatin & etoposide) & XRT
Oct 2013.

Oncology OPD review to discuss MDT decision / plan chemo

Husband concerned over intermittent confusion / deterioration
Unsteady on feet
CT head - No metastasis
S.Na\(^+\) 119 mmol/l, S.Osm 261 mOsmol/kg

Desire to commence chemo asap
But, concern over hyponatraemia
Oct 2013.

Clinically euvoilaemic

\[
\text{S.Na}^+ 119 \text{ mmol/l, S.Osm 261 mOsmol/kg Ur.Na}^+ 56 \text{ mmol/l, Ur.K}^+ 18 \text{ mmol/l, Ur.Osm 307 mOsm/kg)}
\]

Most likely Dx: SIADH 2° to CI & Ca lung.

Furst equation:  \( U/P \text{ electrolyte ratio} = 0.61 \)

500ml fluid restriction

S.Na\(^+\) 130 mmol/l at discharge, and increasing

Definite clinical improvement
Oct 2013.

Commenced chemotherapy
Nausea, malaise, fatigue, altered taste sensation
Unsteadiness, intermittent confusion
Not complying with fluid restriction at home
S.Na\(^+\) 123 mmol/l

“Poor response”  \(\Rightarrow\) D/W Endocrinology

Endocrine SpR –
   Empirically commenced on Tolvaptan 15 mg od
   Fluid restriction stopped
Oct 2013.
Continued on tolvaptan 15mg od
Normal S.Na⁺
Further cycles of chemo proceeded unabated

Sept 2014.
Rechallenge carboplatin / etoposide for tumour progression
S.Na ~131 mmol/l
SST peak cortisol 884 nmol/l
And, so to the theory...
How common is hyponatraemia?

Most common in pt fluid / electrolyte disorder

Incidence - dependent on patient population

- <135 mmol/l in 15 - 30% of hospitalised pts
- more clinically significant
- <130 mmol/l in ~3% of hospitalised pts
  - (7 - 53% institutionalised elderly pts)
  - 40 – 75% pts ‘iatrogenic’ or ‘hospital acquired’

Hyponatraemia is common
Most cases mild and hospital acquired
Hyponatraemia.

Why is hyponatraemia important?

(1) Severe hypoNa<sup>+</sup> (<120 mmol/l) assoc with
   - poor clinical prognosis (mortality RR 3-60 x normoNa<sup>+</sup>)
   - significant morbidity
   - increased length of stay

(2) Mild hypoNa<sup>+</sup> can rapidly progress to severe with Mx other disorders

(3) Over rapid correction can lead to severe neurological morbidity & mortality

(4) Moderate hypoNa<sup>+</sup> associated with under recognised symptoms

Hyponatraemia is associated with poor outcomes, should be managed carefully, and may be adding to pt ‘symptoms’
Salt & water homeostasis.

Serum osmolality (280 – 295 mOsm/l) closely regulated by
- thirst
- vasopressin (ADH) secretion

Thirst, occurs with increases in serum osmolality, to ensure adequate water intake

Vasopressin secreted in response to small increases in serum osmolality
- Increases permeability of renal collecting duct, facilitating reabsorption of water and decreasing plasma osmolality / Na⁺
Pathophysiology HypoNa$^+$.  

Two separate pathogenesis  
(1) Depletion of body solute relative to body water  
   - Excreted or secreted body fluids usually isotonic or hypotonic  
     $\Rightarrow$ increased plasma osmolality.  
   - Marked solute loss results in volume depletion.  
   - HypoNa$^+$ from replacement of fluids with hypotonic solutions  
     (drinking / ivi).  

(2) Excess body water (‘dilutional’)  
   - Impaired renal free water excretion Vs. excessive free water intake.  
   - Kidneys can excrete in excess of 12 litres/dy free water.
Symptoms of HypoNa⁺.

Neurological:
- ‘Hyponatraemic encephalopathy’
- Reflects brain oedema
- Headache, nausea, unsteady gait, falls, disorientation, confusion, obtundation, focal neurological deficits, seizures)

Definite symptoms unclear until Na <125 mmol/l
Rate of fall Na⁺ dictates clinical presentation
Deaths = resp failure after tentorial cerebral herniation & brain stem compression, also non-cardiogenic pulmonary oedema
Aetiology of Hyponatraemia.

(1) Dehydration
   - GI, cutaneous, blood, Na\(^+\) losing nephropathy
   - Diuretics

(2) SIADH

(3) CCF, Nephrosis / Renal Failure, Cirrhosis

(4) Adrenal insufficiency

(5) Hypothyroidism

(6) Pseudohyponatraemia
Adrenal Insufficiency.
Let's start with “Addison’s Disease”.

Adrenal cortical failure (prevalence 1/100,000)

Clinically
- lethargy, general malaise
- GI symptoms
- unexplained wt loss
- postural hypotension
- pigmentation
- acute crises during concomitant illness / stresses

Many patients ‘relatively’ well until intercurrent illness or physical / emotional stress occurs.
Addison’s Disease.

Glucocorticoid, Mineralocorticoid & Androgen Insufficiency

Mineralocorticoid deficiency – Na\(^+\) & water wasting
- Reduced ability to excrete K\(^+\)

Glucocorticoid deficiency – Inability to excrete free water
- Loss of anti-insulin action
- Loss of vascular integrity

Clinically?
- hyponatraemia (GD)
- hypoglycaemia (GD)
- postural hypotension (GD)
- hyperkalaemia (MD)
- dehydration (MD)
HPA axis feedback.

Exogenous Glucocorticoids
Glucocorticoid insufficiency
- i.e. secondary to exogenous steroid therapy
- at risk population ‘supraphysiological’ glucocorticoids > 7 days
- dose dependent
- oral, inhaled, joint, or topical steroids
- central ACTH suppression

So on withdrawal of glucocorticoid Rx?
Or on reducing glucocorticoid Rx to physiological?
Iatrogenic adrenal insufficiency.

Hydrocortisone = cortisol
Cortisol production rates 9-12 mg/day

Prednisolone = 4-5 x Hydrocortisone
Dexamethasone = 20-40 x Hydrocortisone
Fluticasone = 50-60 x Hydrocortisone
How do we manage Addison’s disease?

Acute Management
- iv N/Saline +/- 10% dextrose
- iv hydrocortisone (5-10mg/hr)
- ?mineralocorticoid acutely

Longer Term
- short synacthen test / ACTH
- long-term HC & FC +/- DHEA
- education
And so for iatrogenic AI?

Firstly, be aware of the possibility

- in patients who have recently received steroids
- contribution to non-specific symptoms
- in the setting of hyponatraemia (~25% only)
- diagnosis easiest by SST
And so for iatrogenic AI?

Secondly, prevent ‘crises’
- double the ‘physiological’ glucocorticoid dosage for inter-current illness / stresses

- replacement HC (10/5/5 mg)

- patient education

- recovery generally occurs, but is often delayed
SIADH.
Anti-Diuretic Hormone (ADH).

- ADH / Vasopressin is produced in the hypothalamus and stored in the pituitary.
- Released logarithmically in response to increases in plasma osmolality.
- Once released into the circulation, ADH can activate three GPCR: $V_{1a}$, $V_{1b}$ and $V_2$.
  - $V_{1a}$ – smooth muscle
  - $V_{1b}$ – anterior pituitary (ACTH release)
  - $V_2$ – renal collecting duct
Anti-Diuretic Hormone (ADH).
Syndrome of Inappropriate ADH (SIADH).

- In SIADH, ‘inappropriate’ secretion of vasopressin results in:
  - An inability to excrete dilute urine
  - Retention of water
  - Modest expansion of extracellular fluid (ECF) volume
  - Dilution of serum sodium concentration
  - And ultimately dilutional hyponatraemia
Syndrome of Inappropriate ADH (SIADH).

Most common cause of euvolaemic hyponatraemia
Commonest single cause of hyponatraemia

Diagnosis;
(1) Decreased plasma osmolality <275 mOsm/l
(2) Inappropriate urinary osmolality
   (i.e. greater than maximally dilute ~100 mOsm/l)
(3) Clinical euvolaemia
(4) Elevated urinary sodium excretion (>20 mmol/l)
(5) Absence of other causes of euvolaemic hypoNa+
### Syndrome of Inappropriate ADH (SIADH)

<table>
<thead>
<tr>
<th>Cancers</th>
<th>Pulmonary diseases</th>
<th>CNS disorders</th>
<th>Drugs</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinomas</td>
<td>Infections</td>
<td>Infection</td>
<td>Stimulation of vasopressin release or enhancement of its action</td>
<td>Hereditary Idiopathic Transient</td>
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<td>(eg. lung, oropharynx,</td>
<td>(eg. pneumonia,</td>
<td>(eg. encephalitis, meningitis)</td>
<td>(eg. chlorpropamide, SSRIs, carbamazepine, anti-psychotic drugs</td>
<td>(eg. endurance exercise, general anaesthesia)</td>
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<td>gastro-intestinal tract,</td>
<td>abscess,</td>
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<td>Vasopressin analogues</td>
<td>AIDS</td>
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<td>genitourinary tract)</td>
<td>tuberculosis)</td>
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<td>(eg. desmopressin, oxytocin, vasopressin)</td>
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<tr>
<td>Lymphomas</td>
<td><strong>Asthma</strong></td>
<td><strong>Bleeding and masses</strong></td>
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<td>Sarcomas</td>
<td>Cystic fibrosis</td>
<td>(eg. SAH, brain tumours, head</td>
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<td>COPD</td>
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<td>syndrome)</td>
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</tbody>
</table>
Syndrome of Inappropriate ADH (SIADH).

Management
- Fluid Restriction
- Demeclocycline
  reduces ADH-induced cAMP in collecting ducts
  450 – 1200mg/dy
  dose increases every 3-4 days
  monitor U&E and LFTs
- Vaptans
  block V2 receptors
  first of class ‘tolvaptan’

Most important – Treat underlying cause
Vaptans.
Vaptans.

Non-peptide selective $V_2$ receptor antagonists

Orally and / or intravenously active

Prevent binding of the native hormone without interacting with the site critical for receptor-mediated activation
Tolvaptan.

- specifically targets the $V_2$ receptor, which reduces renal reabsorption of water$^2$
Tolvaptan (Samsca™), potent, once daily, oral, selective V2R antagonist

Approved for Rx of hypoNa⁺ secondary to SIADH

Fluid restriction discontinued before initiation of tolvaptan as increases risk of over-correction

Effectively and predictably raises and maintains serum sodium concentrations as early as 6-8 hours post-dose

Long-term therapy is well-tolerated
Tolvaptan – Practically….

• Treatment initiated at 15 mg once daily
  – Initiated in hospital
  – Prescribed on a daily basis initially
  – Dose may be increased at intervals of ≥ 24 hours, to a maximum of 60 mg/day as tolerated, to achieve the desired serum sodium concentrations
  – During titration, patients should be monitored for serum sodium (6hrly), fluid balance, and volume status
Tolvaptan Vs Fluid Restriction.

Mean (SE) change from baseline in serum sodium (mEq/L)
Tolvaptan – SALT1 & 2.

Mean change from baseline in serum sodium concentration for subjects with SIADH/other

Pooled data from SALT-1 and SALT-2 Phase III trials. Intent-to-treat dataset (OC)
<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Common: polydipsia, dehydration, hyperkalaemia, hyperglycaemia, decreased appetite</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Uncommon: dysgeusia</td>
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<tr>
<td>Vascular disorders</td>
<td>Common: orthostatic hypotension</td>
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<tr>
<td>Gastrointestinal disorders</td>
<td>Very common: nausea</td>
</tr>
<tr>
<td></td>
<td>Common: constipation, dry mouth</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Common: ecchymosis, pruritus</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Common: pollakiuria, polyuria</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Very common: thirst</td>
</tr>
<tr>
<td></td>
<td>Common: asthenia, pyrexia</td>
</tr>
<tr>
<td>Investigations</td>
<td>Common: increased blood creatinine</td>
</tr>
</tbody>
</table>
Tolvaptan – Cost.

- £70 / day
- Infrequent use in LTHT Endocrinology (Cancer, Neurosurgery)

- Proposed use
  - Neurosurgery pts
  - Cancer therapy
  - End of life care
  - Chronic SIADH with regular hospital admissions
Pontine Myelinolysis.
Pontine & Extrapontine Myelinolysis.

Demyelination, not confined to pons!
Present with cognitive, behavioural, and neuropsychiatric disorders

Determined by rate and magnitude of correction of hyponatraemia over first few days.

Associated with increases of >10mmol/l in 24hrs, or 18mmol/l in 48hrs.

May occur whilst Na still subnormal

Independent of method used to correct Na

More frequent in prolonged and severe hyponatraemia (rare if Na > 120 mmol/l).
Assessment & Management.
European Guidelines for Hyponatraemia.

“Clinical practice guideline on diagnosis and treatment of hyponatraemia”


Nephrol Dial Transplant. 2014 Apr;29 Suppl 2:i1-i39

European Society of Intensive Care Medicine (ESICM)
European Society of Endocrinology (ESE)
European Renal Association – European Dialysis and Transplant Association (ERA–EDTA), represented by European Renal Best Practice (ERBP)
Mainstay of SIADH management – Oral urea!
At least seven boxes on algorithm refer to text for Rx
No mention of V$_2$R antagonists (Vaptans)

Complex!

Applicable to UK?
Therefore -

- Need for simplified guideline
- Universal
- Applicable to UK practice
- Aimed at Acute / GIM physicians & Endocrinology trainees

- Consensus group (Feb 2014)
- Aim: To create an algorithm designed to provide simple guidance on the management of hyponatraemia in the UK.
- Final algorithm drafted based on the collective information presented and discussed.
Inpatient hyponatraemia and SIADH management guidance

**HYPONATRAEMIA** [Na⁺] <130 mmol/L

- Consider the context:
  - e.g. known cancer, polydipsia
  - Stop any offending medications:
  - e.g. thiazide diuretics, SSRIs

- Assess patient’s hydration status
- Perform initial immediate investigation panel
  - Glucose
  - Lipids
  - Cortisol
  - Thyroid function
  - Liver function
  - Plasma osmolality
  - Urine osmolality
  - Urine [Na⁺] + [K⁺]

- If poor response:
  - Treat the underlying cause:
    - e.g. cardiac failure, renal failure, liver cirrhosis

- Treat with 0.9% saline
- Consult with Specialist:
  - e.g. Consultant Endocrinologist

- Consider tolvaptan 15 mg od or demeclocycline 150–300 mg
- Tolvaptan:
  - Give single dose of 15 mg and monitor serum [Na⁺] at 2, 4 and 6 hours, and regularly thereafter. Consider second dose at 24 h if appropriate

- Urine [Na⁺] <20 mmol/L: reconsider hypo/hypervolaemia; consider non-renal sodium losses

- HYPOVOLAEMIA
  - Reduced skin turgor
  - Dry membranes
  - Tachycardia
  - Low BP or postural hypotension

- EUVOLAEMIA
  - Confirm hypotonic hyponatraemia
    - i.e. plasma osmolality <275 Osm/kg, urine osmolality >100 Osm/kg

- HYPERVOLAEMIA
  - Oedema
  - Raised JVP
  - LVF
  - Ascites

- Calculate electrolyte-free water clearance using Furst formula:
  - Urine [Na⁺] + [K⁺]
  - Serum [Na⁺]

- Assess response after 24–48 h
  - Re-evaluate

---

**Assessments**
- Urgent management
- Management
- Monitoring

---

*Hypertonic 3% saline can also be administered at 0.5–1 mL/kg/hour with frequent monitoring every 2–4 hours
BP = blood pressure; CNS = central nervous system; CT = computerised tomography; GCS = Glasgow Coma Scale; IV = intravenous; JVP = jugular venous pressure; LVF = left ventricular failure; SIADH = syndrome of inappropriate antidiuretic hormone secretion; SSRI = selective serotonin reuptake inhibitor
Urgent management

Acute symptomatic hyponatraemia
- CNS disturbance
- Confusion
- Headache
- Drowsiness
- Coma / altered GCS
- Seizures
- Encephalopathic

Move to a Level 2 monitored environment

Administration of hypertonic 3% saline*
150 mL IV over 20 min
Repeat after 20 min if no clinical improvement
Recheck serum [Na⁺] at 6, 12, 24 and 48 h for overcorrection (no more than 10 mmol/L in 24 h, 18 mmol/L in 48 h)

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CNS = central nervous system; GCS = Glasgow Coma Scale; IV = intravenous;
Assessments

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- Stop any offending medications
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**Initial immediate investigation panel**

- Glucose
- Lipids
- Cortisol
- Thyroid function
- Liver function
- Plasma osmolality
- Urine osmolality
- Urine $[\text{Na}^+] + [\text{K}^+]$

Assess patient’s hydration status

**EUVOLAEMIA**

- Confirm hypotonic hyponatraemia
  - i.e. plasma osmolality $< 275 \text{ Osm/kg}$, urine osmolality $> 100 \text{ Osm/kg}$

- Check urine $[\text{Na}^+]$

**HYPOVOLAEMIA**

- Reduced skin turgor
- Dry membranes
- Tachycardia
- Low BP or postural hypotension

**HYPERVOLAEMIA**

- Oedema
- Raised JVP
- LVF
- Ascites

- Investigate underlying cause: consider
  - CT chest / abdomen / pelvis / head

- Calculate electrolyte-free water clearance using Furst formula:
  - Urine $[\text{Na}^+] + [\text{K}^+]$
  - Serum $[\text{Na}^+]$

**BP** = blood pressure; **CT** = computerised tomography; **JVP** = jugular venous pressure; **LVF** = left ventricular failure; **SIADH** = syndrome of inappropriate antidiuretic hormone secretion; **SSRI** = selective serotonin reuptake inhibitor
Management and Monitoring

Assess patient’s hydration status

EUVOLAEMIA

HYPOVOLAEMIA
- Reduced skin turgor
- Dry membranes
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HYPERVOLAEMIA
- Oedema
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Treat with 0.9% saline

Treat the underlying cause e.g. cardiac failure, renal failure, liver cirrhosis
Management and Monitoring

**EUVOLAEMIA**

Confirm hypotonic hyponatraemia
i.e. plasma osmolality <275 Osm/kg,
urine osmolality >100 Osm/kg

Check urine [Na⁺]

**Urine [Na⁺] >20 mmol/L: likely SIADH**

Investigate underlying cause: consider CT chest / abdomen / pelvis / head

Calculate electrolyte-free water clearance using Furst formula:
\[
\text{Urine [Na⁺]} + \text{[K⁺]} / \text{Serum [Na⁺]}
\]

Treat the underlying cause e.g. cardiac failure, renal failure, liver cirrhosis

Urine [Na⁺] <20 mmol/L: reconsider hypo/hypovolaemia; consider non-renal sodium losses

Treat with 0.9% saline

<0.5: commence 1.0 L fluid restriction

0.5–1.0: commence 0.5 L fluid restriction

>1.0: fluid restriction unlikely to be effective

Assess response after 24–48 h
Re-evaluate

Consult with Specialist
e.g. Consultant Endocrinologist

If poor response

Consider tolvaptan 15 mg od
or demeclocycline 150–300 mg

Tolvaptan: give single dose of 15 mg and
monitor serum [Na⁺] at 2, 4 and 6 hours,
and regularly thereafter. Consider second
dose at 24 h if appropriate

Aim for target [Na⁺] 130 mmol/L
What are the take home messages?

Hyponatraemia is common and may be contributing significantly to perceived symptoms.

Symptoms are non-specific.

Don’t forget the possibility of ‘iatrogenic adrenal insufficiency’

SIADH can be treated effectively with $V_2R$ antagonists where alternate methods are ineffective, or more urgent correction is required

Care must be taken not to correct hyponatraemia too quickly
Any Questions?