Pathophysiology of water and electrolyte metabolism

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Sudden disaster on a Sunday afternoon ..... 

- 84 years old female, admitted to hospital 12 days earlier because she had had diarrhoea for 3 days
- On admission she looked volume depleted, had low BP (90/50 mmHg)
- Laboratory results: Hgb 9.86 g%, serum Na 134 mmol/l, K 3.0 mmol/l, BUN 21.9 mmol/l, creatinine 182 umol/l
- She got 0.9% NaCl infusion+KCl for 3 days the BP normalized (118/59 mmHg), the labs: Na 141 mmol/l, K 3.6 mmol/l, BUN 4.1 mmol/l, creatinine 86 umol/l
- The gastroenterology team decided to go on with GI work up in order to look for the cause of anemia
Sudden disaster on a Sunday afternoon ..... 

- Scheduled for colonoscopy on Monday (plan to preparing her by Fleet enema on Sunday evening)
- Instruction by the nurse on Sunday morning: „no solid food to eat, only fluids to drink”
- On Sunday morning – complaints free, ambulating, „looked nervous”
- In the afternoon: she suddenly lost her consciousness, had a convulsion, did not respond even to pain, had uncoordinated movements in all her extremities. Repeatedly vomited.
Sudden disaster on a Sunday afternoon ..... 

- Urgent labwork: serum Na 117 mmol/l, K 2,9 mmol/l, BUN 2,4 mmol/l, creatinine 98 umol/l
- Urinary osmolality 431 mOsm/kg, urinary Na 164 mmol/l, K 44 mmol/l hrs, 900 ml/12 hrs
- Brain CT: 
  - no major abnormality can be seen
- She remained unconscious in the next day: 
  Neurological examination:
  - no primary neurological abnormality, 
  EEG: diffuse functional cortical abnormality
Sudden disaster on a Sunday afternoon ..... 

- Why was she mildly hyponatremic on admission?
- Why had she severe hyponatremia 12 days later?
- What do you think about the urinary osmolality of 431 mOsm/kg?
- And about the urinary Na of 164 mmol/l?
- What is your suggestion for treatment on the day of admission?
- What would you give on the 12th day? How much?
Hyponatremia

ADH secretion + Water intake

Both need to be present

Why ???

Why is ADH secreted in spite of hypoosmolality?
Where is the water coming from?

Is this an acute or a chronic condition?
ADH secretion

- In physiologic conditions
  - increased osmolality
  - increased serum Na

- In pathophysiologic conditions
  - stress, anxiety, pain, fever, nausea, vomiting
  - severe hypovolemia due to
    - fluid loss
    - diuretic use
  - effective volume depletion
  - SIADH
  - medications
Treatment on the first day

- The major stimulus for ADH was the volume depletion
- 0.9% NaCl infusion shuts off the stimulus for ADH secretion
- How do you know this?
  The urine with high osmolality (evidence for ADH secretion) changes to less concentrated urine
  → the patient becomes able to excrete free water
  → the low serum osmolality and low serum Na are increasing and get normalized
- Hypertonic Na infusion is unnecessary and dangerous
Treatment on the 12th day

- Acute, severe hyponatremia, causing convulsion, coma, vomiting → very likely cerebral edema
- Urine osmolality: 431 mOsm/kg - proves strong influence of ADH (likely due to stress, anxiety, nausea)
- Lots of fluid intake according to the instructions
- Urine Na: 164 mmol/l means - no volume depletion
- Treatment: 3% NaCl infusion
- How much?
Treatment on the 12th day

- Weight of the patient: 72 kg. Body water: 42 l
  In order to elevate her serum Na by 1 mmol/l, she needs 42 mmol Na
  In order to elevate serum her Na by 5 mmol/l, she needs 210 mmol Na
  It means 408 ml of 3% NaCl infusion

- Follow urinary Na loss and replace it

- Check electrolytes frequently
Treatment on the 12th day

- She got 300 ml 3% NaCl infusion (154 mmol) and 4 g KCl
- 4 hours later serum Na 119 mmol/l, K 3,2 mmol/l
- During Sunday night 300 ml 3% NaCl infusion (154 mmol) and 4 g KCl
- On Monday morning 300 ml 3% NaCl infusion (154 mmol)
- In 24 hours: serum Na 130 mmol/l, K 3,9 mmol/l
- Urinary losses in 24 hrs: 230 mmol Na and 62 mmol K
- In summary she got 462 mmol Na in the 1st 24 hrs
- Next day: serum Na 134 mmol/l, she regained consciousness
- Two days later: serum Na 140 mmol/l
Acute hyponatremia

ADH secretion + Water intake

Both need to be present

Why is ADH secreted in spite of hypoosmolality?
- stress, anxiety, pain, fever, nausea, vomiting,
  typically in a perioperative situation

Where is the water coming from?
- hypotonic fluid intake, very often iv. infusions
Generation of EFW - Desalination

1000 ml Salsol infusion
154 mmol Na⁺

1000 ml Salsol infusion
154 mmol Na⁺

Body

Urine 1000 ml
Na⁺ excretion 308 mmol

Persistent ADH action
No reason to retain NaCl

Balance:

Water intake: 2000 ml
Na⁺ intake 308 mmol

Excreted free water: 1000 ml
Excreted Na⁺: 308 mmol

1 L electrolyte free water is retained in the body, which causes hyponatremia
69 yrs female, in her past medical history:
- 1990. Resection of malignant lung tumor
- For 2 years hypertension, osteoporosis
- Meds: indapamide, aspirin, carvedilol, vitamin D, Calcium suppl.

2008. october
- Dizziness, headache, unsteadiness, repeated falls
- Once she invited guests, treated them, made conversation, but later did not remember these events

SeNa
- oct. 3. 141,  dec. 19. 126,
- oct. 29. 119,  febr. 20. 120 mmol/l.
- nov. 17. 124,
More tests than thoughts....

Tests because of her complaints (oct-febr):
- head CT, 2x head MRI, neurosurgical consultation (some traumatic contusions)
- chest XR and CT, mammography, abdominal US, carotid art. doppler scan, neurological examination

Modification of the therapy:
- Indapamide changed to ramipril+hydrochlorothiazide
- Increased salt and fluid (!) intake suggested (although the patient did not wish to drink much)

What is wrong with this lady?
Not so difficult....

- Febr. 20. Nephrology consultation: discontinue the thiazide, continue increased salt intake but limit fluid intake
- March 10. Free of complaints - SeNa 140 mmol/l.
The most frequent causes of hyponatremia

Clayton et al. Q.J.Med 2006

- Hyponatremia was found in 108 of the 9622 patients admitted to internal medicine department in 6 months

- Etiology
  - Thiazide diuretics - 29 cases
  - Congestive heart failure - 27 cases
  - Liver cirrhosis - 21 cases
  - In further cases: volume depletion, medications, malignancies, lung- and cerebral diseases, hypothyroidism, Addison disease, hypoNa postoperatively, primary polydipsia and chronic renal failure

- During the hospitalization 20% of the patients died
Risk factors for thiazid-induced hyponatremia

Chow et al. Q.J. Med 2003

- Between 1996-2002 223 thiazide caused hyponatremic patients were observed
- SeNa: 98-128 mmol/l (mean 116±7 mmol/l)
- Length of treatment 1-4479 day! (mean 105 day)
  - 42,8% indapamide, 15,4% HCT+triamterene
  - 16,1% HCT, 8,4% bendrofluazide
  - 17,3% HCT+amiloride,
- Thiazides were administered mainly for hypertension
- Risk factors for developing hyponatremia:
  - age, low body weight, hypokalemia
Pathomechanism of thiazid-induced hyponatremia

- In most cases ADH secretion could not be explained by volume depletion!
- When thiazide is taken, the medulla can achieve high concentration – little ADH is enough to produce concentrated urine
- Decreased urinary dilution capacity in the elderly
- Increased fluid intake due to increased thirstiness (?)
- Decreased salt intake – advised medically sec.to HTN (?)
- Na\(^+\)-K\(^+\) transcellular shift in hypokalemia
- Activation of AQP-2 channels in cortical tubules due to thiazides – individual sensitivity (?)
Do cirrhotic patients need sodium in hyponatremia?

- 70 yrs old male, treated on an internal medicine department. He is a regular alcohol drinker, has liver cirrhosis, oedema on the legs and huge ascites.
- On admission: serum Na 132 mmol/l, K 4.2 mmol/l, BUN 5.7 mmol/l, creatinine 82 umol/l.
- Initial treatment: 100 mg spironolactone, 160 mg furosemide, 50 mg ethacrynic acid, 50 mg hydrochlorothiazide, 3 g KCl.
- In three days BW 115 → 111 kg, Na 132 → 125 mmol/l, creatinine 82 → 126 umol/l.
- Treatment: furosemide discontinued, others continued, + 5 g NaCl in Ringer infusion.
Do cirrhotic patients need sodium in hyponatremia?

- In the next three days: BW → 120 kg, SeNa → 117 → 109 mmol/l, creatinine → 270 umol/l,
- Even more NaCl given
- Consultation asked for nephrology service because oliguria, deteriorating renal functions: SeNa 112 mmol/l, K 3.8 mmol/l, BUN 8.8 mmol/l, creatinine 307 umol/l
  Urinary Na excretion 2 mmol/day, K 8.6 mmol/day
- How would you manage this patient?
Hyponatremia in cirrhotic patients

Splanchnic vasodilatation, ↓ systemic vascular resistance, ↓ MAP

Baroreceptor activation - „effective volume depletion”

↑ secretion of the „hypovolaemic hormones”

Renin → Ang.II.  ADH  Norepinephrine

Further factors contributing to hyponatremia:
- overgenerous diuretic treatment
- too much fluid intake (e.g. Beer drinkers)
Hyponatremia in congestive heart failure

↓ cardiac output, ↓ systemic blood pressure

Baroreceptors sense low perfusion pressure
(in the carotid sinus, aortic arch, afferent arterioles in the kidneys)
„effective volume depletion”

↑ secretion of the „hypovolaemic hormones”

Renin → Ang.II.    ADH    Norepinephrine

Other factors causing hyponatremia:
Low cardiac output, high level of Ang II. → increased thirstiness
Disturbed free water clearance – effects of the „hypovolaemic hormones”

Ang.II
Norepinephrine

↓ GFR

Isosomolar Na and water reabs.

Free water delivery into the distal nephron ↓
→ free water excretion ↓

AQP-2 expression

↑ free water reabs.

ADH
Hyponatremia in cirrhotic patients

- Severity of hyponatremia is proportional to the prognosis
- Correction of hyponatremia does not change the hemodynamical, pathophysiological abnormalities
- Mild hyponatremia usually does not cause major complaints, do not have to be treated (≈>125mmol/l)
- Treatment: decrease fluid intake in order to achieve negative fluid balance
- „Delicate” diuretic administration, mainly loop diuretics (if peripheral edema present, ↓ BW: by 1-2 kg/d, if only ascites: <0,5 kg/d)
- Hypertonic saline infusion is contraindicated !!
- Vasopressin receptor antagonists: aquaretics (vaptans)
Therapy in CHF

- Survival is proportional to the degree of hyponatremia
- Its correction does not improve the prognosis of CHF
- ACEI/ARB
  - Cardiac output improves
  - ACEI decreases ADH’s effectivity in the cortical collecting duct, therefore water reabsorption ↓
  - Decreased thirstiness
- Moderate fluid restriction
- Administration of moderate doses of loop diuretics
- Vasopressin receptor antagonists: aquaretics (vaptans)
A case of SIADH

- 66 years old male, ALL diagnosed 9 months ago
- Got monthly bolus cytostatic treatments
- Developed aspergillus pneumonia - Rx intaconazole
- Admitted secondary to feeling unwell, weak, dizzy, but he was ambulating, can properly communicate
- Labs: Na 117 mmol/l, K 3.5 mmol/l, Cl 85 mmol/l, bicarb 23 mmol/l, BUN 6.5 mmol/l, creatinine 75 umol/l, BS 8.3 mmol/l, serum osmolality 237 mOsm/kg, urinary Na 83 mmol/l, osmolality 456 mOsm/kg, normal TSH
- According to his chart: serum Na 123-133 mmol/l previously
- Why does he have ADH? Acute or chronic?
Inappropriate ADH secretion - SIADH

- **Malignancies**
  - small lung cell carcinoma
  - prostate, uterus cc.
  - pancreas, duodenum cc.
  - leukemia, lymphoma

- **Medications**
  - dDAVP, oxytocin, NSAID
  - antidepressants,
  - narcotics, nicotine
  - cytostatics
  - chlorpropamide
  - carbamazepine

- **Central nervous syst.dis.**
  - Tumors, abscess
  - infections
  - Demyelinization diseases
  - SAH, trauma

- **Lung diseases**
  - TBC, aspergillosis
  - pneumonia, abscess
  - obstructive lung disease
  - ventilation
Vaptans

- Vasopressin receptor antagonists – increase electrolyte-free water excretion
- Conivaptan (V1a and V2), tolvaptan, satavaptan, lixivaptan (V2 receptor antagonists)
- Indicated (in general) in euvolemic and hypervolemic hyponatremia
- Contraindicated in hypovolemic hyponatremia
- Overcorrection of hyponatremia has to be avoided!
- Very expensive drugs
Tolvaptan – EVEREST trial
Gheorghiade M et al., JAMA 2007. 297:1332

- Short and long term administration of tolvaptan
  - randomised controlled trial
  - 4133 patients admitted with chronic heart failure
- Body weight, dyspnea, edema ↓, serum Na ↑ more in patients who received tolvaptan
- But no effect on mortality, comparing to placebo
- Mental functioning showed small but significant improvement in the tolvaptan group
Two multicenter RCTs for 30 days

Tolvaptan 225 pts, placebo 223 pts with SIADH, CHF, and cirrhosis

Serum Na increased more in the tolvaptan group

Hyponatremia recurred after tolvaptan was discontinued

Patients in the tolvaptan group had increased thirst, dry mouth, increased urination
Hyponatremia in chronic renal failure

- **Our case:** 72 years old lady, regularly seen on clinic
  - eGFR 10 ml/min
  - Nausea, vomiting, feeling unwell
  - Se Na 129 mmol/l, urine output 3400 ml/day

- **On the next visit:**
  - Se Na 135 mmol/l
  - urinary osmolality 284 mOsm/kg
  - urine output 2800 ml/day

- **Why was she hyponatremic?**
What does the maximal urinary diluting capacity mean?

- Healthy persons:
  - Minimal urine osmolality: 50-80 mOsm/kg
  - Average solute excretion: 600-900 mOsm/day (300-450 mmol Na, K + the anions, and 300-450 urea)

- How much can we drink without the risk of hyponatremia?
  
  \[
  \text{Solute excretion} / \text{diluting capacity} / \text{L} \\
  \begin{align*}
  &900 \text{ mOsm and } 50 \text{ mOsm/kg } = 18 \text{ L} \\
  &600 \text{ mOsm and } 80 \text{ mOsm/kg } = 7.5 \text{ L} \\
  &200 \text{ mOsm and } 50 \text{ mOsm/kg } = 4 \text{ L}
  \end{align*}
  \]

- Beer potomania („Tea and toast” hyponatremia):
  - Low protein and salt intake, therefore low osmolar excretion and too much fluid intake
Hyponatremia in chronic renal failure

- The urine is „isostenuric” ≈ 300 mOsm/kg
- The kidneys are not able to dilute significantly better (nor concentrate)
- If the daily solute excretion 900 mOsm – maximally 3 L fluid can be excreted, without causing hyponatremia
- But on low protein and low salt diet the daily solute excretion ↓, therefore exaggerated fluid intake can cause hyponatremia
- Therapy: adjust fluid intake to the actual diluting capacity of the kidneys
What kind of i.v. infusion has to be given in hypernatremia?

- 81 yrs old male patient, admitted to hospital because of volume depletion and pneumonia. He was febrile, desoriented.

- Lab results: serum Na 156 mmol/l, K 5,0 mmol/l, BUN 22 mmol/l, creatinine 173 umol/l, glucose 6,1 mmol/l.

- Chest XR: pneumonia and pulmonary congestion

- Initial treatment: 500 ml of Ringer lactate infusion and 500 ml 5% glucose infusion

- Was this appropriate? What kind of change do you expect in serum Na concentration?
What kind of i.v. infusion has to be given in hypernatremia?

**Next morning:**
- Serum Na 157 mmol/l, osmolality 330 mOsm/kg
- Urinary Na 40 mmol/l, K 48 mmol/l, osmolality 463 mOsm/kg
(24 hrs collection could not be done)
What kind of i.v. infusion has to be given in hypernatremia?

- **Na balance**
  - the patient excreted 40 mmol/l sodium,
  - intake by RL: 67 mmol
  (Ringer lactate contains 132 mmol/l)

- **Treatment on the following day**
  1500 ml 5% glucose infusion, and he was eating and drinking a little
  Serum Na 159 mmol/l

- **Why? What can we do now?**
What kind of i.v. infusion has to be given in hypernatremia?

- Checking again the urinary excretion: Na 11 mmol/l, K 9,5 mmol/l osmolality 439 mOsm/kg
- He was excreting very little Na
- He was not able to increase his urine osmolality
- We gave 40 mg furosemide i.v. and 2500 ml 5% glucose infusion daily
- The urinary Na excretion increased to **52 mmol/l**, K excretion to 30,2 mmol/l
- The serum Na decreased gradually and in 3 days normalized to **137 mmol/l**
Sodium balance in diabetes insipidus

Balance:

Water intake: 4000 ml/24 hr
Na\(^+\) intake 272 mmol
Excreted water: 4000 ml/24 hr
Excreted Na\(^+\): 140 mmol/24 hr

The patients retains 33 mmol Na\(^+\) by each L of infusion
In 24 hours 132 mmol Na\(^+\) surplus created in the body.

4000 ml Rindex 5 infusion
68 mmol/l Na\(^+\)

Body

4000 ml urine
Na\(^+\) concentration 35 mmol/l, ozmolality 150 mOzm/kg
Potassium disorders
Hypokalemia – where does this huge amount of K go?

- A 62 yrs old female
- PMHx: collagen colitis – she had been well for years
- She presented with profuse, watery diarrhoea, several times daily. In the last days nausea and vomiting also occurred
- On admission: severely volume depleted, very weak, completely anuric, BP 60/40 mmHg.
Hypokalemia – where does this huge amount of K go?

- Labs on admission:
  Na 124 mmol/l, K 1,8 mmol/l, BUN 31,5 mmol/l, creatinine 665 umol/l

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</table>
Hypokalemia – where does this huge amount of K go?

- Why did she need so much K?
  \(83 \text{ g} = 1079 \text{ mmol}\)

- Did this patient have renal K wasting tubulopathy?
Hypokalemia – first step in differential diagnosis

- Urinary K excretion
  - In our patient: 19.5 mmol/day
  - 18.8 mmol/day
Hypokalemia – where does this huge amount of K go?

- Body weight of the patient: 60 kg
  Extracellular water: 10 l
  Intracellular water: 20 l

- K content of EC: 10\times 4 = 40 \text{ mmol}
  K content of IC: 20\times 150 = 3000 \text{ mmol}
An other hypokalemic patient...

- 48 years old male
- PMHx: hypertension since his age of 30
- His mother, his sister and his son also have HTN
- Serum potassium between 2.5-2.9 mmol/l for years
- Meds on the first consultation: 20 mg amlodipin, 2x20 mg enalapril+hydrochlorothiazide, 4 mg prasosin, 2x2 g KCL
- Labs: serum Na 145 mmol/l, K 2.9 mmol/l, CN 7.7 mmol/l, creatinine 100 umol/l
- What kind of tests would you order?
An other hypokalemic patient ...

- 24 hr urinary Na: 262 mmol/day
  24 hr urinary K: 104 mmol/day
- Blood gas analysis:
  pH 7.46
  HCO_3^- 28.8 mmol/l
  pCO_2 41 mmHg
- What is the differential diagnosis?
An other hypokalemic patient...

- Renin and aldosterone levels - repeatedly normal
- RAS - excluded
- Glucocorticoid overproduction – serum cortisol normal
- Rx: spironolactone – no change
- What is your diagnosis and how would you treat this patient?
Principal cell in the cortical collecting duct

- Continually open ENaC
- Familiar HTN
- Suppressed renin and aldosterone
- Rx: amiloride, triamterene

Liddle syndrome
Is this an emergency?
Life threatening hyperkalemia

- 82 years old female with HTN, DM, and CRF
- Serum creatinin earlier 150 umol/l
- Rx: 20 mg lisinopril, 20 mg spironolactone, 5 mg amiloride, 50 mg hydrochlorotiazide, 100 mg metoprolol, trimetroprim-sulfamethoxasol for one week
- Extremely week, unable to walk, than respiratory insufficiency developed
- Labs: serum Na 133 mmol/l, K 10.0 mmol/l, Cl 102 mmol/l, HCO3 18 mmol/l, kreat 265 umol/l, CN 31.5 mmol/l, Vc 26.4 mmol/l, urinary K 16 mmol/l.
- How many reasons did she have for hyperkalemia?
Inhibitors of renal potassium excretion

- Decreased Na\(^+\) delivery

- GFR
  - acute on chronic renal insufficiency

- Renin
  - metoprolol

- Ang II.
  - ACEI

- aldosterone
  - spironolactone

- ENaC
  - amiloride
  - trimetoprim

(Lack of insulin
- decreased K intake by cells)