

The significance of hyponatraemia: clinical considerations and novel therapeutic strategies

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Clinical significance of hyponatraemia

- Hyponatraemia is the most common electrolyte disorder in hospitalised patients
 - In a prospective study between 2002 and 2003, hyponatraemia was present on admission in 14.5% of 98,411 hospitalised patients¹
- Hyponatraemia is associated with:
 - Increased morbidity
 - Gait and attention impairments, which may lead to falls and fractures and subsequent increased hospitalisation^{2,3}
 - Increased length of hospital stay⁴⁻⁶
 - Increased risk of death (in hospital and 1 year and 5 years post discharge), even in mild hyponatraemia¹
 - Mortality is 60 x greater in severe hyponatraemia (< 120 mmol/l), even in the absence of symptoms, compared with normonatraemic patients⁷

1. Waikar SS, et al. *Am J Med.* 2009;122:857–865.
2. Renneboog B, et al. *Am J Med.* 2006;119:71.e1–8.
3. Kenge FG, et al. *Q J Med.* 2008;101:583–588.
4. Sherlock M, et al. *Clin Endocrinol.* 2006;64:250–254.

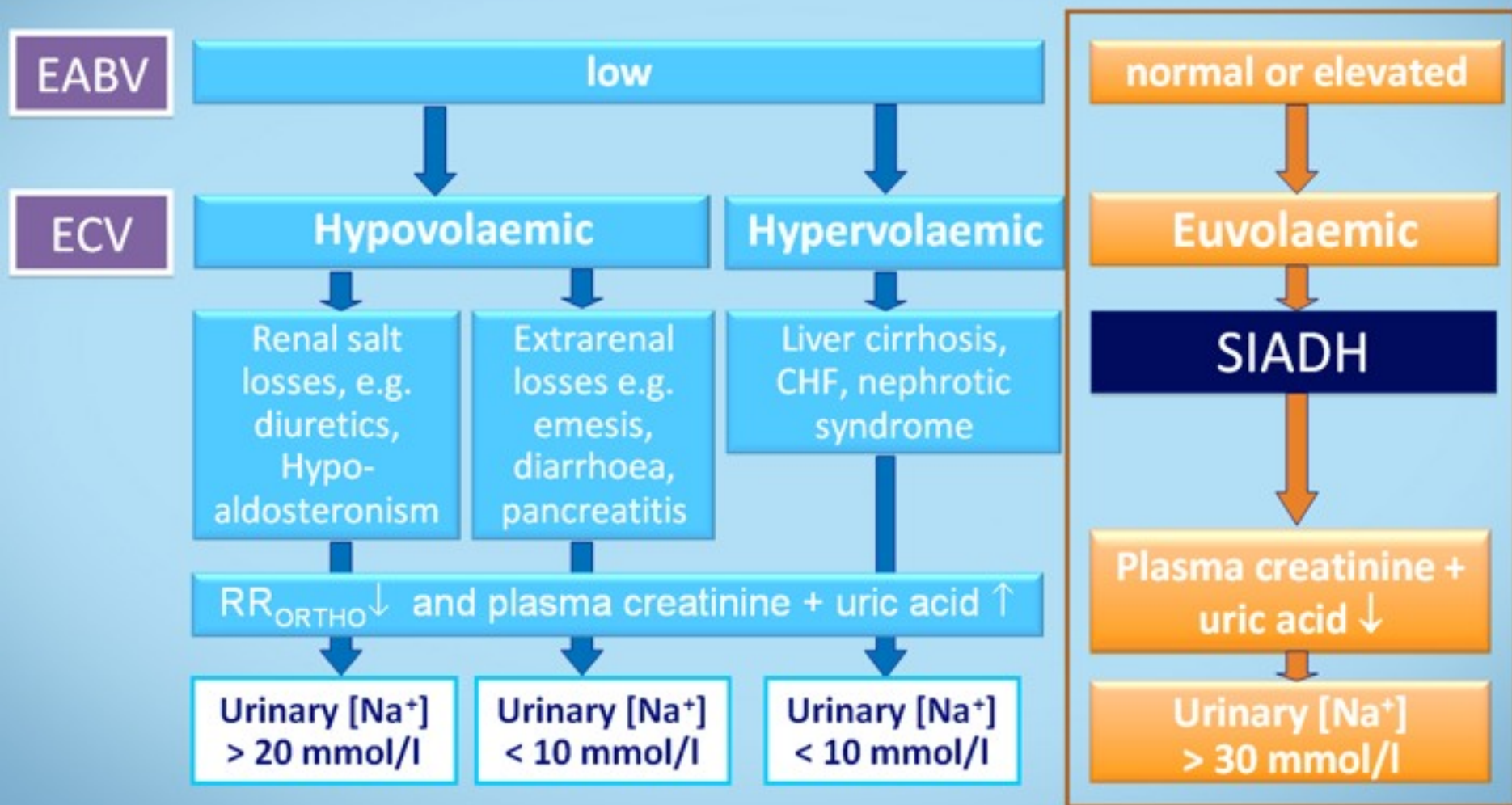
5. Sherlock M, et al. *PMJ.* 2009;85:171–175.
6. Gill G, et al. *Clin Endocrinol.* 2006;64:246–249.
7. Anderson RJ, et al. *Ann Intern Med.* 1985;102:164–168.

Symptoms of hyponatraemia

Hyponatraemic encephalopathy



Differential diagnosis of hyponatraemia



EABV = effective arterial blood volume, ECV = extracellular blood volume

Criteria for the diagnosis of SIADH¹

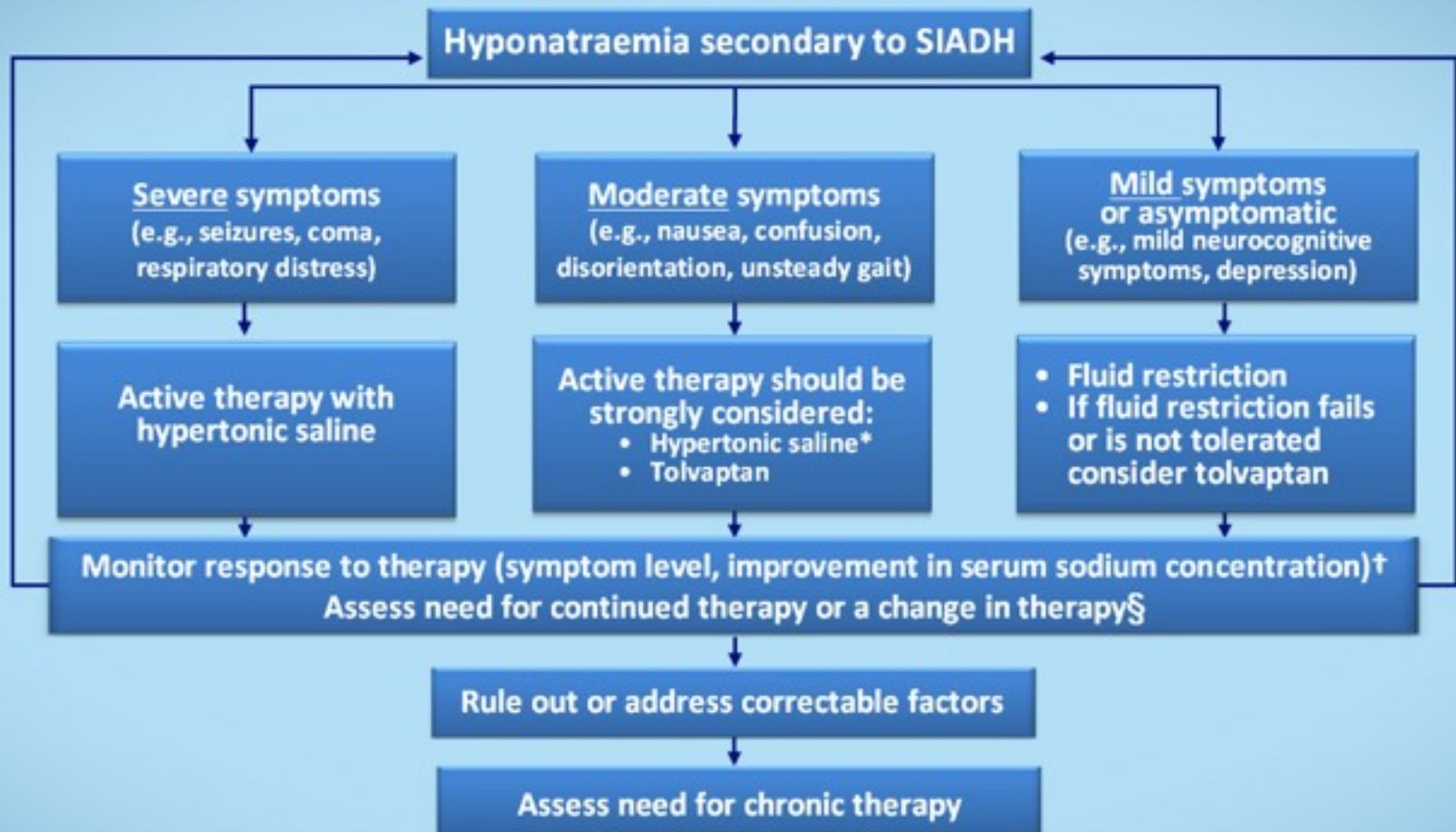
Essential	Supporting
• Hyponatraemia (plasma sodium < 135 mmol/l) • Decreased measured plasma osmolality (< 275 mOsm/kg H₂O) • Urinary osmolality > 100 mOsm/kg H₂O during hypo-osmolality • Clinical euvolaemia – No clinical signs of contraction of extracellular fluid (e.g., no orthostasis*, tachycardia, decreased skin turgor or dry mucous membranes) – No clinical signs of expansion extracellular fluid (e.g., no oedema or ascites) • Urinary sodium > 30 mmol/l with normal dietary salt intake** • Normal thyroid and adrenal function determined by both clinical and laboratory assessment • No use of diuretic agents within the week prior to evaluation	• Plasma uric acid <4 mg/dl (< 0.2 mmol/l) • Blood urea nitrogen <10 mg/dl (< 3.6 mmol/l) • Fractional sodium excretion > 1%; Fractional urea excretion >55%*** • Failure to improve hyponatraemia after 0.9% saline infusion • Improvement of hyponatraemia with fluid restriction

* Orthostatic changes in blood pressure and pulse rate are defined as a ≥ 20 mm decrease in systolic BP and/or as a ≥ 20 bpm increase in pulse rate upon going from a supine to a standing position

** Although high urine sodium excretion generally occurs in patients with SIADH, its presence does not confirm the diagnosis, nor does its absence rule out the diagnosis; urine sodium can also be high in renal causes of solute depletion such as diuretic use or Addison's disease, and conversely some patients with SIADH can have low urinary sodium if they become hypovolaemic or solute depleted, which are conditions sometimes produced by imposed sodium and water restriction

*** Fractional sodium excretion = (urinary sodium/plasma sodium) / (urinary creatinine/plasma creatinine) X 100;
 Fractional urea excretion = (urinary urea/plasma urea) / (urinary creatinine / plasma creatinine) X 100

Hyponatraemia secondary to SIADH: Treatment algorithm



* Although moderate symptoms can be treated with either hypertonic saline or tolvaptan, if the hyponatraemia is known to be acute (i.e., <48 hrs duration) hypertonic saline is preferred because of the possibility of rapid progression to more severe symptoms.

† Patients receiving active therapy should have serum [Na⁺] monitored at least every 6 hours during initial days of therapy.

§ Correction of hyponatraemia with active therapies should be limited to < 12 mmol/l in 24 hours and to < 18 mmol/l in 48 hours.

Case study: presentation, history and physical examination

- 63 year old man complaining of:
 - General fatigue, headaches, loss of appetite, nausea, problems remembering dates and names, becoming lost sometimes and unsteadiness of gait
- History
 - 2 months of fatigue and weight loss (2 kg)
 - Smoked half pack of cigarettes/day for 40 years
 - Drank 0.5 l wine/day for 40 years
 - No surgery or medication (aspirin occasionally)
- Physical examination
 - CT and chest X-ray already performed and normal
 - Patient in poor physical condition; not corresponding to athletic build (height 190 cm, weight 90 kg)
 - BP 130/80 mmHg
 - HR 80/min
 - Lymph nodes not palpable
 - No anaemia, jaundice or peripheral oedema

Case study: laboratory values and investigation into underlying cause

- **Laboratory values:**
 - Serum sodium: 114 mmol/l
 - Serum osmolality: 230 mOsmol/kg
 - Creatinine: 0.59 mg/dl
 - Uric acid: 3.1 mg/dl
 - Urine osmolality: 720 mOsmol/kg
 - Urine sodium: 86 mmol/l
 - Other laboratory values normal
- **Diagnosis: Chronic euvolaemic hyponatraemia with moderate symptoms**
- Thoracic CT scan: Small mid thoracic retrocardial pulmonary mass and bilaterally enlarged hilar lymph nodes
- Abdominal CT scan: Normal
- Bronchoscopy: Mild compression of the left bronchus
- Biopsy: Small cell carcinoma of the lung
- **Diagnosis: Small cell carcinoma of the lung, limited disease, and paraneoplastic SIADH with chronic euvolaemic hyponatraemia**

Case study: treatment

- Fluid restriction
 - Patient improved moderately (serum sodium increased to 120 mmol/l after 1 week) but did not tolerate sufficient fluid restriction (< 800 ml)
- Platin-based chemotherapy recommended
 - In order to improve the condition of the patient before chemotherapy, tolvaptan therapy was initiated
- Tolvaptan initiated at a dose of 15 mg/day
 - Water restriction maintained at 1–1.2 l/day
 - Serum sodium increased to 124 mmol/l on day 1, 126 mmol/l on day 2, 130 mmol/l on day 3 and was 135 mmol/l on day 7
 - Patient's symptoms resolved completely
- Chemotherapy with etoposide/cisplatin started on day 7 leading to partial remission after 2 cycles
- Tolvaptan paused after 18 days of therapy at a serum sodium of 143 mmol/l
 - Sodium remained stable at a level of 135–138 mmol/l with fluid restriction only

Prescribing information

Samsca®

Presentation: Tablets containing 15 mg or 30 mg of tolvaptan.
Indication: Treatment of adult patients with hyponatraemia secondary to syndrome of inappropriate antidiuretic hormone secretion (SIADH). **Dosage:** To be initiated in hospital due to need for dose titration with close monitoring of serum sodium and volume status. For oral use, 15 mg once daily, increasing to a maximum of 60 mg once daily as tolerated to achieve desired serum sodium correction. No dosage adjustment for elderly or in mild to moderate renal or hepatic impairment. No information is available in severe renal or hepatic impairment. There is no experience in children and adolescents under the age of 18 years. **Contraindications:** Hypersensitivity to any component of Samsca. Anuria. Volume depletion. Hypovolaemic hyponatraemia. Hypernatraemia. Patients who can not perceive thirst. Pregnancy. Breastfeeding. **Warnings and precautions:** Tolvaptan has not been studied in a setting of urgent need to raise serum sodium acutely. For such patients, alternative treatment should be considered. Caution should be exercised to ensure patients have adequate access to water and not become overly dehydrated. Urinary outflow must be secured to avoid risk of developing acute urinary retention. Patients should be closely monitored for serum sodium and volume status, particularly in those with renal and hepatic impairment. Rate of sodium correction should be managed carefully in patients at risk of demyelination syndromes (e.g. hypoxia, alcoholism, malnutrition). In patients who develop too rapid a rise in serum sodium (> 12 mmol/L/24 hours), tolvaptan should be discontinued and administration of hypotonic fluid should be considered. Pseudohyponatraemia should be excluded prior and during

treatment with tolvaptan, particularly in hyperglycaemic patients. Tolvaptan may cause hyperglycaemia, therefore diabetic patients treated with tolvaptan should be managed cautiously, in particular poorly controlled type II diabetes. Tolvaptan contains lactose as an excipient; patients with galactose intolerance, Lapp lactase deficiency or glucosegalactose malabsorption should not take this medicine. Caution when driving vehicles or using machines, occasionally dizziness, asthenia or syncope may occur. **Drug interactions:** Caution with: co-administration with CYP3A4 inhibitors, inducers and substrates, and digoxin. Concomitant use with hypertonic saline is not recommended. **Undesirable effects:** The following adverse reactions were reported in clinical trials in hyponatraemia: Very common ($\geq 1/10$): Thirst, nausea. Common ($\geq 1/100$ to $< 1/10$): Dry mouth, constipation, polydipsia, dehydration, hyperkalaemia, hyperglycaemia, decreased appetite, orthostatic hypotension, ecchymosis, pruritis, pollakiuria, polyuria, asthenia, pyrexia increased blood creatinine. Uncommon ($\geq 1/1000$ to $< 1/100$): Dysgeusia. See Summary of Product Characteristics for further details and other undesirable effects. **Overdosage:** There is no information on overdosage but profuse and prolonged aquaresis is anticipated. Adequate fluid intake must be maintained. **Legal category:** POM. **Marketing Authorisation numbers:** SAMSCA 15 mg (EU/1/09/539/001). SAMSCA 30 mg (EU/1/09/539/003). **Marketing Authorisation Holder:** Otsuka Pharmaceutical Europe Ltd., Hunton House, Highbridge Business Park, Oxford Road, Uxbridge, Middlesex, UB8 1HU, UK. Further information from: OtsukaMedicalEurope@otsuka-europe.com. **Date of preparation of prescribing information:** August 2009.

Please report Adverse Drug Reactions to

Otsuka Pharmaceutical Europe Ltd. Pharmacovigilance Department on telephone :
+44 (0) 1895 207 100 (including out-of hours), fax : +44 (0) 1895 207 115