Acute Symptomatic Hyponatraemia – A Practical Approach

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Abstract

Hyponatraemia is the commonest electrolyte abnormality yet is poorly understood. Symptoms are dependent on the rate of onset and severity. The presence of features suggestive of neurological dysfunction should be regarded as a medical emergency and treated actively. The risk of not treating outweighs that of over aggressive management.

This article concentrates on the immediate management of the patient presenting acutely with severe symptomatic hyponatraemia, and is illustrated by a case recently presenting to our department. The patient who is incidentally found to be hyponatraemic in the context of another presenting illness, or presenting with more minor, non-specific symptoms presents different challenges to the admitting clinician, which will be dealt with in a future edition of the journal.

Introduction

Hyponatraemia reflects an abnormal ratio of sodium to water and is defined as a serum sodium concentration of less than 135 mmol/L.

Despite being the commonest electrolyte abnormality in clinical practice[4–6] and associated with significant morbidity and mortality,[3,4] it is poorly understood and incorrect management may be detrimental.

This disorder has a wide clinical spectrum of presentation (Figure 1) which is critically dependent on the rapidity of onset and degree of hyponatraemia.

Symptoms result from cerebral oedema which occurs as a result of reduced extracellular osmotic forces. Homeostatic mechanisms are in place to compensate for this but in the setting of an acute (within 48-hours) drop in plasma sodium concentration may be overwhelmed. Coma and seizures usually occur only with acute reduction of the sodium concentration to less than 120 mmol/L.[16] Conversely, a more gradual fall in sodium concentration to levels as low as 110 mmol/L over days or weeks may be asymptomatic.

Treatment varies depending on whether features of neurological involvement are present. Absolute serum values and the chronicity of hyponatraemia are less important.[18–21]

In this article we present a case of acute, symptomatic hyponatraemia and review the literature to provide recommendations on safe and effective therapy in this setting.

Case Report

A 24-year-old Caucasian male presented as an emergency following two witnessed vacant episodes within five hours. He was described, without warning, to mumble and drool and subsequently develop features of central cyanosis. Each episode was self-limiting within two minutes and he was well in between. There was no history of meningism or systemic upset.

Ten days earlier he had sustained a head injury associated with transient loss of consciousness and

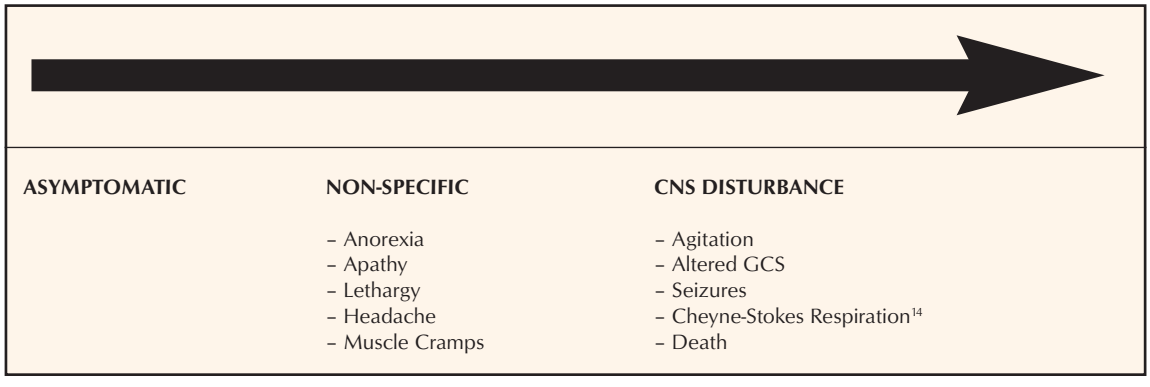


Figure 1. Gradation of symptoms encountered in cases of hyponatraemia.

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bloody ottorrhoea but no neurological deficit following an alleged assault. A CT-scan of his brain had revealed an acute right frontal haematoma without any mass effect associated with basal skull and left petrous pyramidal skull fractures in addition to a left maxillary haemosinus and the presence of blood in the ipsilateral middle ear. He was admitted under the care of the surgical team and his case discussed with the regional neurosurgical centre. A conservative strategy was adopted and he was discharged after four days. He had no significant medical history prior to this.

During assessment he had two generalised seizures in close succession which were self-terminating within two minutes. He had a prolonged post-ictal period with a reduced level of consciousness and required an oropharyngeal airway. He was normoglycaemic and normotensive throughout with downgoing plantar reflexes and in-tact pupillary reflexes.

An urgent CT-brain demonstrated a resolving right frontal haematoma with no evidence of any further acute intracranial haemorrhages or cerebral oedema.

Blood tests were unremarkable with the exception of marked hyponatraemia with a serum sodium concentration of 113 mmol/L. This had been normal six days earlier.

Discussion

In clinical practice it may be difficult to determine whether hyponatraemia is acute or chronic. Indeed, those with a chronically reduced serum sodium level may develop an acute reduction and become symptomatic. Irrespective of the duration of biochemical derangement management is determined by symptom severity rather than absolute serum values.[18–21]

The most significant consequence of hyponatraemia is cerebral oedema and subsequent brainstem herniation. In this setting a conservative approach to management is likely to be more detrimental than the sequelae of overly rapid serological correction, namely central pontine myelinosis (CPM). Brain damage is more likely in untreated patients.[2,8,15,23,30] However it is important to note that CPM – an osmotic demyelination syndrome – is more typical in the setting of rapidly corrected *chronic* hyponatraemia.

We will focus on patients presenting with neurological dysfunction which should be regarded as a medical emergency and warrants aggressive intervention.[18,21] Management can be divided into four steps:

Step 1 – Resuscitation

Supportive care and termination of seizure activity (if present) is the initial priority. This involves assessment and appropriate management of the airway, breathing and circulation. In some situations intubation with an endotracheal tube is required and controlled hyperventilation should be considered to reduce intracranial pressure. Anaesthetic expertise is desirable under these circumstances. If intravenous fluid therapy is administered, hypotonic fluids should be avoided as these may exacerbate cerebral oedema.

If seizure activity is present and does not spontaneously resolve parenteral benzodiazepines should be administered. Hypoglycaemia and other biochemical anomalies (in particular hypokalaemia, hypomagnesaemia and hypocalcaemia) should be excluded.

Comprehensive neurological assessment should be undertaken and an urgent CT-Brain scan considered.

Step 2 – Correct Hyponatraemia

Safe biochemical correction with **hypertonic saline** is crucial and should occur in a critical care environment where vigilant monitoring is feasible. No consensus exists over the optimal rate of correction as there is little evidence from randomised controlled trials. There is a general agreement that serum sodium can be increased by 6-10 mmol/L (at a rate of 1.5 -2.5 mmol/L/hr) over the first four hours or until symptoms abate.[9,13,18,23–26,29–32] Serum sodium levels should be measured hourly until the patient is stable.[23] Using animal models, the correction rate in the first 24-hours has been shown to be more important than the maximum rate in any given hour.[27,28] In an attempt to avoid the consequences of overly rapid correction, treatment should aim to increase plasma levels by no more than 10–15 mmol/L in the first 24-hours[25,26] and by no more than 15–20 mmol/L in the first 48-hours.[9,13,18,25,26,29,30–32] The goal should be to achieve a serum sodium concentration of 120-125 mmol/L.[24]

When hypertonic saline is used, the quantity of sodium required to achieve the desired change in serum sodium concentration can be estimated using the following equation:

$$\textbf{Sodium deficit} = \textbf{TBW} \times (\textbf{desired } [Na^+] - \textbf{actual } [Na^+])$$

Where TBW (Total Body Water), is calculated as body weight (kilograms) multiplied by 0.6 or 0.5 in adult males and females respectively.

MEDICATIONS ASSOCIATED WITH HYPONATRAEMIA

Acetazolamide, amiloride, amphotericin, aripiprazole, atovaquone, **thiazide diuretics**, amiodarone, basiliximab, angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors, **carbamazepine**, carboplatin, carvedilol, celecoxib, **cyclophosphamide**, clofibrate, desmopressin, donepezil, duloxetine, eplerenone, gabapentin, haloperidol, heparin, hydroxyurea, indomethacin, ketorolac, levetiracetam, **loop diuretics**, mirtazapine, mitoxantrone, nimodipine, oxcarbazepine, opiates, oxytocin, pimozide, propafenone, proton pump inhibitors, quetiapine, sirolimus, ticlopidine, tolterodine, vincristine, **selective serotonin re-uptake inhibitors**, sulfonylureas, trazodone, tolbutamide, venlafaxine, vincristine, zalcitabine, and zonisamide.

Figure 2. Medications associated with hyponatraemia (most frequent are shown in bold).

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INVESTIGATION OF HYPONATRAEMIA	
AT PRESENTATION	**FOR LATER CONSIDERATION**

– Serum osmolarity
– Urine osmolarity
– Urine spot sodium concentration
– Serum glucose, lipids & liver biochemistry
– Thyroid function tests
– Static adrenal function tests (random cortisol)
– Consider urgent CT-Head
	– Dynamic adrenal function tests:
	  – Peak cortisol during short SYNACTHEN test
	– Imaging:
	  – Plain chest radiograph
	  – Consider CT-Thorax
	  – Consider CT-Brain

Figure 3. Investigation of hyponatraemia.

In the case presented the initial sodium deficit, based on a weight of 80kg and desired serum sodium concentration of 123 mmol/L, was estimated as follows:

i) SODIUM DEFICIT
– (80 × 0.6) × (123–113) = Deficit of 480 mmol

ii) INFUSION RATE
– Locally only 1.8% hypertonic sodium chloride solution was available (308 mmol of sodium per litre, which approximates to 0.3 mmol millilitre) →
– Infusion commenced at 75 ml/hr for 4-hours (90 mmol) & 50ml/hr for 20-hours (300 mmol) which equated to a total sodium load of 390 mmol in the first 24-hours

In general, 300 ml of 3% or 600ml of 1.8% hypertonic saline over six hours (approximately 150 mmol of sodium) is a reasonable initial regime in most adults with symptomatic hyponatraemia.

In addition to hypertonic saline, **loop diuretics** may be employed to enhance free water clearance in the setting of hyperosmolar (> 300mOsmol/kg) urine.[32] Resultant natriuresis is subsequently replaced in a smaller volume. Such combination therapy can result in a rapid elevation in plasma sodium levels and requires vigilant monitoring.

There may be a role for anti-diuretic hormone / arginine vasopressin (V_2) receptor antagonists. These have been shown to induce a selective water diuresis with little urinary electrolyte loss and hence they are also termed 'Aquaretics'. Further research is needed to determine their therapeutic use.

Finally, potential culprit medications (see Figure 2) should be temporarily discontinued.

Step 3 – Steroid Therapy

Parenteral glucocorticoid therapy should be considered in sick patients given the possibility of underlying Addison's Disease. This intervention may be life saving and is unlikely to cause harm.

Step 4 – Determine Cause

Once the patient has stabilised, the main priority becomes establishing the underlying aetiology of hyponatraemia as this will ultimately dictate the long-term management strategy. This will necessitate a review of the clinical scenario including history and examination with an emphasis on volume status.

DIFFERENTIAL DIAGNOSIS OF HYPO-OSMOLAR HYPONATRAEMIA		
	NON-RENAL **Urine [Na^+] < 30 mmol/L**	**RENAL** **Urine [Na^+] > 30 mmol/L**
1. Hypovolaemic	GI loss (diarrhoea & vomiting, stomas) Dermal losses (sweating, burns)	Renal Loss (diuretic, salt losing nephropathy, mineralcorticoid deficiency, cerebral salt wasting)
2. Euvolaemic	Decreased solute intake	SIADH (Δ of exclusion) Hypoadrenalism Hypothyroidism Post-TURP* Primary polydipsia Excessive hypotonic fluids
3. Hypervolaemic	Congestive cardiac failure Cirrhosis (with ascites) Nephrotic syndrome	Acute & chronic renal failure
*** TURP – Transurethral resection of the prostate gland.**		

Figure 4. Differential diagnosis of hypo-osmolar hyponatraemia.

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GUIDELINE FOR THE MANAGEMENT OF SYMPTOMATIC HYPONATRAEMIA

- Hyponatraemia is the commonest electrolyte abnormality;
- **Symptomatic hyponatraemia**, manifesting with neurological dysfunction, is a ***Medical Emergency*** and warrants aggressive intervention;
- The consequences of delaying treatment is more likely to be detrimental than overly rapid correction!

STEP 1 – RESUSCITATION
A – Airway – Consider endotracheal intubation (anaesthetic expertise desirable);
B – Breathing – Avoid hypoaxaemia; Consider hyperventilation to reduce ICP;
C – Circulation – Avoid hypotonic fluids (this will exacerbate cerebral oedema).

In the event of a **SEIZURE** which does not spontaneously resolve:

- Administer 5–10 mg diazepam rectally or intravenously;
- Consider loading with intravenous antiepileptic medication e.g. phenytoin;
- Exclude hypoglycaemia and hyponatraemia / kalaemia / calcaemia;
- Post-ictally perform a full neurological examination, maintain on regular neurological observations and consider an urgent CT-Brain.

STEP 2 – AGGRESSIVE VIGILANT CORRECTION OF HYPONATRAEMIA (PREFERABLY IN A CRITICAL CARE ENVIRONMENT)
- The ultimate goal is to achieve a serum sodium concentration between **120-125 mmol/L;**
- Recommended maximum rate of correction: **10 mmol/L in 24-hours** & **18 mmol/L in 48-hours;**
- In general, 300 ml of 3% or 600ml of 1.8% hypertonic saline over six hours (approx. 150 mmol of sodium) is a reasonable initial regime in most adults with symptomatic hyponatraemia.

1) – HYPERTONIC SALINE (> 0.9% NaCl) INFUSION
- 1.8 % Saline – Contains 308 mmol/L of NaCl
- 2.7% Saline – Contains 462 mmolL of NaCl
- 3% Saline – Contains 514 mmol/L of NaCl

The *quantity of sodium* required and hence the *rate of infusate* (of a given concentration) to achieve the desired change in serum sodium concentration can be estimated using the following equation:

$$\textbf{Sodium deficit} = \textbf{TBW} \times (\textbf{desired } [Na^+] - \textbf{actual } [Na^+])$$

Where TBW (Total Body Water), which represents the osmotic space of distribution of plasma sodium, is calculated as body weight (kilograms) multiplied by 0.6 or 0.5 in adult males and females respectively.

e.g. Thus, if the initial aim of therapy in a symptomatic hyponatremic 60 kg woman is to raise the plasma sodium concentration from 110 to 120 mmol/L, then the sodium deficit for initial therapy is estimated to be 300mmol (i.e. 0.5 x 60 x (120–110). This can be given as 600 mL of hypertonic (3%) saline (which contains approximately 500 mmol of sodium per litre, or one mmol of sodium per 2 mL).

2) – DISCONTINUE POTENTIAL CULPRIT / AGGRAVATING MEDICATIONS
Common offenders to look for include: thiazide diuretics, carbemazipine & SSRI's.

STEP 3 – STEROID THERAPY
Parenteral glucocorticoid therapy (**100–200mg IV Hydrocortisone**) should be considered in sick patients given the possibility of underlying Addison's Disease. This intervention may be life saving and is unlikely to cause harm.

STEP 4 – BE A DETECTIVE: DETERMINE THE UNDERLYING CAUSE
– This is crucial to the long-term management strategy and becomes the main priority once the patient is stable and involves:

1) **Review history**
2) **Repeat examination (emphasis on assessment of fluid status)**
3) **Investigations:**

AT PRESENTATION
- Serum osmolarity*
- Urine osmolarity*
- Urine spot sodium concentration*
- Serum glucose, lipids & liver biochemistry
- Thyroid function tests
- Static adrenal function tests (random cortisol)
- Consider urgent CT-Head

FOR LATER CONSIDERATION
- Dynamic adrenal function tests:
  - Peak cortisol during short SYNACTHEN Test
- Imaging:
  - Plain chest radiograph
  - Consider CT-Thorax & Brain

* Most important initial investigations:
- **Serum osmolarity** is almost always low in cases of true hyponatraemia;
- **Urine osmolarity** indicates whether water excretion is impaired and in most cases is inappropriately high (> 100 mOsmol/L). This is the typical picture of SIADH;
- The most useful single test, when coupled with an assessment of hydration status, is the **urine spot sodium test** which allows distinction between renal (Urine $[Na^+]$ > 30mmol/L) and non-renal salt loss (Urine $[Na^+]$ < 30mmol/L).

Figure 5. Recommendations for the management of symptomatic hyponatraemia.

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There is a myriad of investigations, as outlined in Figure 3, which have been sub-divided into those which ought to be carried out at presentation following the diagnosis of hyponatraemia and those that might be required at a later stage.

In true hyponatraemia, serum osmolarity is almost always low. Causes of pseudohyponatraemia (including hyperlipidaemia, hyperglycaemia and hyperproteinaemia) therefore should be considered in normo-osmolar and hyperosmolar states.

Urine osmolarity indicates whether water excretion is impaired and in most cases is inappropriately high (> 100 mOsmol/L). This is the typical picture in the syndrome of inappropriate ADH secretion (SIADH).

However, although usually measured, these two tests alone are rarely discriminant. The most useful single test, when coupled with an assessment of hydration status, is the urine spot sodium test which allows distinction between renal and non-renal salt loss. Figure 4 demonstrates the differential diagnosis of hypo-osmolar hyponatraemia according to these variables.

Case Conclusion & Final Thoughts

The subject in the case presented was managed by the medical team in a critical care environment. His sodium deficit was calculated and he subsequently benefited from an infusion of 1.8% hypertonic saline. His serum sodium concentration was measured 4-hourly and increased by 14-mmol/L in the first 24-hours and normalised within 48-hours.

In the acute setting he was loaded with intravenous phenytoin given the theoretical possibility that a structural pathology rather than his biochemical derangement was the focus underlying his seizures. This was discontinued after 24-hours and he was discharged without maintenance therapy after 4-days. We found no guidance in the literature with regard to the use of antiepileptic medications in this setting. He was advised to inform the DVLA, and not to drive pending their definitive recommendations.

He remained fit free with normal biochemistry when reviewed at his three month follow up appointment.

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