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Hyponatraemia

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ABSTRACT Hyponatraemia is present in 15–20% of non-selected emergency admissions to hospitals in the UK. It is associated with increased mortality and morbidity as well as increased duration of stay, independent of the cause for admission. Hyponatraemia is therefore common and important, driving the need for a rational but practical management strategy. This must encompass a stratified approach based on clinical presentation, balancing diagnostic uncertainty and the relative merits of different interventions to achieve the best outcome.

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INTRODUCTION

Sodium is the major circulating cation. Plasma concentration is maintained within a tight physiological range. The regulation of sodium balance, water balance and circulating volume are linked and are best viewed as overlapping, co-ordinated neuro-humoral systems.

Plasma sodium concentration reflects the balance between sodium and water content. Each component reflects the balance of intake and output. This approach can be used to develop a framework for classifying hyponatraemia by aetiology. While such a framework has merits, it is important to recognise that hyponatraemia is often multifactorial.

Regulation of plasma volume and osmolality

Given that water content is a key determinant of plasma sodium concentration, it is intuitive that a breakdown in the relationship between water intake and water excretion could be one of the mechanisms underpinning hyponatraemia. The physiology of water balance thus serves to highlight the pathophysiological processes through which hyponatraemia can develop.

Water resorption by the distal nephron involves the movement of water from the lumen of the collecting duct into the renal interstitium. This requires both an osmolar gradient and functioning aquaporin 2 (AQP2) water channels on the luminal surface of collecting duct cells. The expression of AQP2 is dependent on the posterior pituitary hormone vasopressin (AVP).

Plasma osmolality is the major determinant of AVP secretion. Above a functional osmolar threshold of some 285 mOsm/kg, AVP secretion increases linearly in response to increments in plasma osmolality. If fluid volumes greater than those demanded by thirst are consumed, AVP secretion is suppressed to very low levels (<0.3 pmol/l), at which the kidney is capable of excreting 15–20 l of urine in 24 hours. Ingestion of fluid volumes in excess of this results in progressive lowering of plasma sodium.

Given the key role of AVP in reducing renal free water excretion, it is easy to see that inappropriate excess production of this hormone could lead to the development of hyponatraemia through haemodilution. While such inappropriate AVP production is one of the key mechanisms of hyponatraemia, AVP is an important agent in mediating hyponatraemia in other circumstances too.

TABLE 1 Classification of hyponatraemia

Pseudohyponatraemia		**Reduced renal free water clearance**	
• Hyperglycaemia • Non-physiological osmolyte		Hypo-volaemia	• Drugs • Renal failure • Portal hypertension and ascites • Hypoalbuminaemia • Sepsis and vascular leak syndromes • Central salt wasting • Fluid sequestration
Sodium depletion			
Renal loss	• Diuretics • Salt-wasting nephropathy • Hypoadrenalism • Central salt wasting		
Extra-renal loss	• Gut loss		
Excess water intake		Other	• Cardiac failure • Nephrotic syndrome • Hypothyroidism • Hypoadrenalism • Hypopituitarism • Syndrome of inappropriate antidiuresis (SIAD) • Nephrogenic SIAD • Excess use of AVP analogues (desmopressin [DDAVP] oxytotics)
• Dipsogenic DI • Sodium-free, hyposomolar irrigant solutions • Dilute infant feeding formula • Inappropriate intravenous fluid therapy (excess hypotonic fluid in relation to water excretion; or incorrect solute content)			

Hypotension and circulating volume depletion also stimulate AVP secretion (baro- and volume regulation). Indeed, non-osmoregulated AVP release can occur below the standard osmolar threshold. Hypotension or volume depletion can thus lead to persistent reduction in renal free water clearance despite ensuing hyponatraemia. AVP secretion in this context is physiological and can both initiate and maintain significant hyponatraemia if the deficit in circulating volume persists. This is a common mechanism for hyponatraemia in clinical practice.

AETIOLOGY OF HYPONATRAEMIA (see Table 1)

Intravascular volume depletion

Intravascular volume depletion from long-term diuretic use can produce significant hyponatraemia of 105–125 mmol/l. Because hyponatraemia may develop slowly, patients can be relatively asymptomatic. Those on thiazide diuretics are particularly at risk as these agents produce solute, and thus plasma volume loss, without limiting renal concentrating ability. Renal water resorption capacity is not affected. Volume-stimulated AVP release can produce profound hyponatraemia in this context. While loop diuretics lead to significant solute loss, their site of action leads to a reduced intramedullary solute concentration gradient. Maximal renal concentrating ability is impaired, and water resorption produced by the action of volume-stimulated AVP is limited. Inhibitors of renin–angiotensin system (RAS) action can also cause hyponatraemia through an effective reduction in circulating volume.

Portal hypertension, congestive cardiac failure and hypo-albuminaemia can all reduce effective circulating volume independent of drug treatment and all can produce hyponatraemia through stimulating non-osmoregulated AVP production and renal water resorption, even in the context of excess total body sodium.

Central salt wasting

This acquired primary natriuresis is a rare cause of hyponatraemia with hypovolaemia. The underlying mechanism(s) remains unclear, but may involve increased release of natriuretic peptides and/or reduced sympathetic drive. Central salt wasting (CSW) is seen following a variety of neurosurgical situations. Diagnosis hinges on the natural history of the process: the development of hyponatraemia is preceded by natriuresis and diuresis with ensuing clinical and biochemical features of hypovolaemia. Central salt wasting is a particular concern for the neurosurgical patient in whom autoregulation of cerebral blood flow is disturbed and in whom small reductions in circulating volume can reduce cerebral perfusion. Syndrome of inappropriate antidiuresis (SIAD) can occur in the same group of patients. As management of the two conditions is diametrically opposed, it is important to make the correct differential diagnosis.

TABLE 2 Syndrome of inappropriate antidiuresis: diagnostic characteristics

Hyponatraemia
Urine Osm >100 mOsm/kg • sub-maximum dilution
Urine Na+ > 20 mmol/l
Absence of • hypotension and hypovolaemia • non-osmotic stimuli for AVP release • oedema • adrenal failure • hypothyroidism

TABLE 3 Syndrome of inappropriate antidiuresis: sub-types

Type	Characteristics of AVP release
A	• AVP release independent of plasma osmolality
B	• ↓ Osmotic threshold for AVP release • Osmoregulation around ↓ osmolar set point
C	• Failure to suppress AVP at low osmolality • Normal response to osmotic stimulation
D	• Normal osmoregulated AVP release • Unable to excrete water load

Excess hypotonic fluid intake

The administration or absorption of hypotonic fluids at a rate that exceeds renal free water excretion will inevitably result in hyponatraemia. This can be seen with oral fluid intake (dipsogenic diabetes insipidus), intravenous fluid therapy and the absorption of hypotonic irrigating fluids following surgery to the lower renal tract.

Syndrome of inappropriate antidiuresis

In SIAD there is a failure to maximally suppress AVP secretion as plasma osmolality falls below the normal osmotic threshold for AVP release. Absolute AVP values may not be particularly elevated. As patients continue to drink, persistent antidiuresis produces dilutional hyponatraemia. A diagnosis of SIAD involves the exclusion of volume depletion and other endocrine causes of reduced free water excretion (see Table 2). While emphasis is often placed on urine osmolality exceeding plasma osmolality, osmolar criteria for SIAD are met simply if urine is not maximally dilute in the face of coincident hyponatraemia (urine >100 mOsm/kg in adults).

The majority of patients with SIAD are euvolaemic on clinical examination. This reflects two factors: the difficulty in identifying mild abnormalities of volume status on clinical examination and the homeostatic response to persistent SIAD. Syndrome of inappropriate antidiuresis can result in a negative sodium balance; urine sodium concentration is often above 80 mmol/l. This natriuresis may serve to limit volume expansion and is also important when considering the differential diagnosis

EDUCATION

TABLE 4 Drugs commonly associated with SIAD

Antidepressants	Tricyclic antidepressants SSRIs
Dopamine antagonists	Metoclopramide Prochlorperazine Antipsychotics
Anticonvulsants	Carbamazepine Phenytoin Sodium valproate
Opiates	

of CSW. Four distinct patterns of AVP release have been characterised in SIAD (see Table 3).

Many drugs used in everyday clinical practice cause SIAD, and drug histories are an important part of the clinical assessment of patients presenting with hyponatraemia (see Table 4). Hyponatraemia secondary to SIAD is found in many patients taking anticonvulsants. Hyponatraemia can develop within a few days of commencing treatment with selective serotonin reuptake inhibitors (SSRIs).

Exercise-associated hyponatraemia (EAH)

Extreme endurance exercise produces significant non-osmoregulated AVP release and reduced renal blood flow. Extreme endurance exercise is thus an antidiuretic state. If endurance athletes maintain a fluid intake in excess of free water clearance, hyponatraemia will ensue. This can be further complicated if there is aggressive fluid resuscitation in the event of collapse. The odds ratio for developing hyponatraemia is positively correlated with the length of time taken to complete the event and weight gain over the course of the event. The latter clearly implicates water intake in excess of water loss. Athletes need to be advised to follow their thirst as they run rather than simply taking on fluid.

Nephrogenic SIAD

The action of AVP on renal water excretion is mediated by the G-protein-coupled type 2 AVP-receptor (V2-R). Loss of function mutations of the V2-R are the cause of X-linked nephrogenic diabetes insipidus. Recent studies have identified the reciprocal phenotype: mutations in the V2-R that are constitutively activating, leading to AVP-independent but V2-R-mediated antidiuresis with persistent hyponatraemia.

MANAGEMENT: THE ISSUES

Principles and overview

While hyponatraemia can be life-threatening, chronic hyponatraemia can be tolerated very well even when profound. This diversity poses a challenge in management: clinicians must balance the clinical efficacy of any intervention with the potential adverse impact of both the intervention and persisting hyponatraemia.

Hyponatraemia leads to discrete adaptations within the central nervous system (CNS) that aim to minimise brain swelling and preserve neuronal function. The initial response is an efflux of low molecular weight inorganic osmolytes from glial cells into the extracellular space/cerebrospinal fluid. The timescale of this response is over hours. If hyponatraemia persists, the generation and efflux of organic osmolytes follow. This latter process occurs over days. Both responses reduce intracellular osmolality in an effort to limit net water movement into brain cells. Hyponatraemia of a magnitude that exceeds the capacity of this adaptive response, or develops at a rate that exceeds the rate of adaptation, is likely to be associated with significant neuronal dysfunction and hence symptoms. Adaptive responses are critical factors in determining the approach to intervention. Rapid correction of hyponatraemia to which longer-term brain adaptation has occurred can result in significant osmolar stress to neurones and trigger osmotic demyelination.

The difficulty with many published approaches to the management of hyponatraemia lies in the translation to clinical practice. Volume overload and volume depletion can be apparent on clinical examination or become apparent within hours of presentation. However, in many cases it is difficult to determine volume status on clinical grounds. Drugs used for co-morbid conditions can make the interpretation of diagnostic testing for volume status difficult or impossible. Management guidance based on duration of hyponatraemia is equally problematic. In the majority of patients it is not possible to determine the duration of the problem. Moreover, pre-existing co-morbidities may make it difficult to be clear what contribution the electrolyte disturbance is making to the clinical picture.

While balancing diagnostic uncertainty and the risks and benefits of different management strategies must temper the clinician's response, they need not paralyse it. Rather, they should focus the clinician on the task of prioritisation and identifying the appropriate therapeutic target: reversing or reducing morbidity and mortality associated with hyponatraemia while avoiding complications of treatment. The patient with mild morbidity does not require a non-specific intervention associated with a risk that exceeds that of a more conservative approach. In this situation, there may well be the time to further the differential diagnosis such that a tailored intervention, associated with a lower risk of adverse effects, is possible.

Conversely, the patient presenting with seizure or significant coma requires a different approach; a conservative strategy could result in exposure to the risk of worsening neurological morbidity that exceeds the risk of intervention. In this scenario there may not be time to reach a definitive diagnosis of aetiology before action is required. However, the aim of management should not be achieving a normal plasma sodium level. Rather, it should

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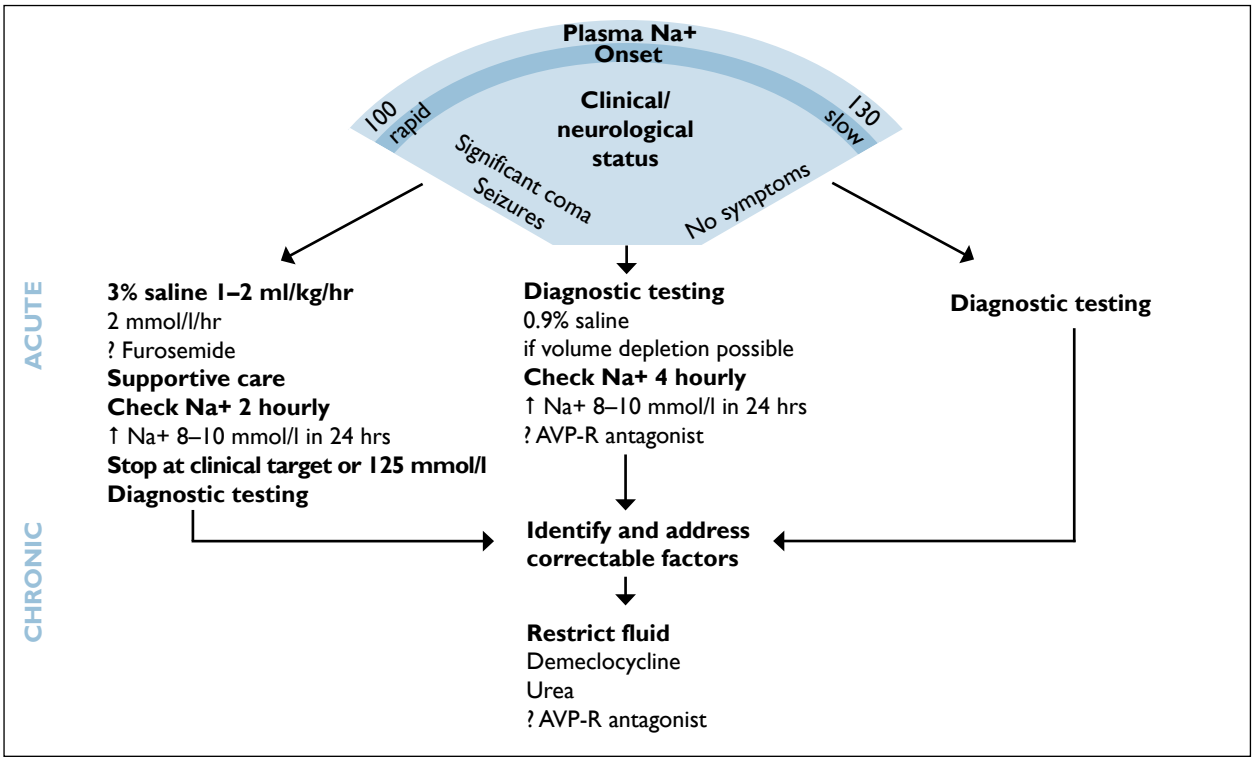

FIGURE 1 Algorithm for the management of hyponatraemia.

be achieving a plasma sodium level that reverses or reduces morbidity (e.g. stops seizures, improves coma) at such a rate that minimises risk of osmotic demyelination. There must be a stratified approach based on clinical presentation, balancing influences to achieve the best outcome (see Figure 1).

General and supportive measures

History and examination are key in the clinical approach. These will provide insights into the aetiology, rate of development, clinical impact and contributing co-morbidities, all factors important in a patient-focused approach to management. The appropriate clinical environment for the management of hyponatraemia is the one that matches the clinical needs of the patient. Management of hyponatraemia in a patient with significant neurological morbidity in whom plasma sodium is being raised over hours requires close clinical and biochemical observation. This is best achieved in a high-dependency setting. Cerebral oedema and coma associated with hyponatraemia may need supportive management with assisted ventilation. The use of mannitol in this situation can complicate the monitoring of biochemical response as it introduces another osmolyte that clinicians need to be aware of when interpreting electrolyte profiles.

Data suggest that an increase in plasma sodium of no more than 8–10 mmol/l/24 hours is safe. Target rates of change expressed as mmol/l/hr are not helpful as they set an expectation of fixed incremental change and move the focus away from clinical endpoints. There may be situations where a relatively rapid rise in plasma sodium of 2–4 mmol/l over 2–4 hours is needed to reduce intracerebral pressure in the acute setting. This approach is appropriate as long as this rate of change is not maintained and the 24-hour limit is not exceeded. Plasma sodium may rise faster than 2 mmol/l/hr during 'autocorrection' of hyponatraemia when an underlying cause has simply been removed, for example a correction of glucocorticoid insufficiency or withdrawal of excess desmopressin. Osmotic demyelination can still occur in these circumstances. It is important to consider actively controlling the rate of rise of plasma sodium in such situations.

Patients with mild or moderate symptoms and signs

The situation is such that the clinician may have time to make a diagnosis, identify and address contributing factors if possible and then, if needed, introduce a focused intervention based on aetiology (e.g. glucocorticoid replacement; see Table 5). The majority of patients will have circulating volume depletion or SIAD. Where these are due to drug treatments, the removal of the causal agent may be sufficient to normalise sodium. There will be some cases where the causal agent cannot be removed or where there is an alternative diagnosis.

Fluid challenge in hypovolaemic hyponatraemia

Mild to moderate hypovolaemia can be difficult to diagnose clinically and low urine sodium excretion (<20 mmol/l) may be unreliable as a diagnostic test in the face of diuretic use or renin-angiotensin system blockade. If volume depletion is suspected, a moderate intravenous fluid challenge with 0.5–1 l N-saline over 2–4 hours may be both diagnostic and therapeutic.

TABLE 5 Diagnostic testing in hyponatraemia

Purpose	Diagnostic test
Clinical baseline	Plasma Na+ Weight Plasma osmolality Urine osmolality
To confirm hypovolaemia	Lying and standing blood pressure Full blood count Plasma urea and creatinine Plasma glucose Plasma urate Serum albumin and liver function Urine Na+
To exclude endocrine causes	Plasma cortisol If <450 nmol/l, consider short synacthen test Free thyroxine and thyroid-stimulating hormone
To exclude other causes	Consider sepsis screen
To investigate basis of SIAD	Chest X-ray

Fluid restriction

Fluid restriction of 0.5–1 l/day is a reasonable initial intervention when excess plasma water is suspected and when the clinical condition is not critical. The higher the baseline urine osmolality, the less likely is fluid restriction to be effective. In patients with primary polydipsia, reduction in fluid intake remains the most reasonable approach. All fluids need to be included in the restriction. As SIAD is associated with negative sodium balance, sodium intake needs to be maintained. Several days of restriction may be required before sodium levels rise and a negative fluid balance needs to be confirmed through appropriate monitoring.

Patients with significant coma or seizures

Hypertonic sodium chloride

Treatment with hypertonic sodium chloride addresses the reduction of plasma sodium concentration simply and directly. It is preferable to 0.9% saline as it allows more sodium to be given more quickly and with less volume. However, it is not without problems. There are numerous models with which to estimate total body water excess or total body sodium deficit in hyponatraemia. The utility of these models in day-to-day practice is limited if the concept of partial correction to clinical endpoints is accepted and further compromised by the use of asymmetric correction rates, with a proportionately larger increase in plasma sodium of some 2–4 mmol/l in the first 1–4 hours of intervention followed by a slower rise of 4–6 mmol/l in the following 20 hours.

An alternative stepped approach using the clinical and biochemical impact of a 100-ml bolus of 3% sodium chloride (with the aim of increasing plasma sodium by 2 mmol/l increments) can be used.

Avoidance of over-correction is critical. Intervention with hypertonic fluid should be stopped when the defined clinical target or a sodium concentration of 125 mmol/l is reached, whichever is first. Increasing plasma sodium to 125 mmol/l is likely to reduce the risk of significant neurological deterioration while minimising the risk of precipitating osmotic demyelination. The rate of change of plasma sodium must remain within the limits of 8–10 mmol/l per 24 hours. Hypertonic sodium chloride (3%) has largely replaced 5% sodium chloride. If hypertonic sodium chloride cannot be given safely, it should not be given.

Management of persistent hyponatraemia

Hyponatraemia may persist or recur after initial intervention. It is important that the differential diagnosis is reviewed and the basis for intervention reconsidered. However, SIAD and chronic volume depletion may require alternative approaches. In SIAD, fluid restriction may be only partly effective or may prove non-sustainable. In chronic persisting volume depletion, liver or cardiac dysfunction may persist and drug therapy exacerbating hyponatraemia may need to continue. Clinical decisions may have to balance the merits of incremental intervention with those of tolerating mild, persisting hyponatraemia.

Demeclocycline and lithium

Demeclocycline is effective in the management of hyponatraemia of SIAD. It produces a form of nephrogenic diabetes insipidus and so increases renal water loss, even in the presence of high concentrations of AVP. Treatment is 600–1,200 mg/day in divided doses. There is a lag time of some 3–4 days in onset of action. Dose adjustment needs to take this into account. Renal function needs to be monitored closely and treatment stopped if significant renal impairment develops. Lithium has similar effects to demeclocycline. The effect of lithium is less consistent and it has more adverse effects.

Urea

Urea can be used to treat persisting hyponatraemia of SIAD. Active orally at doses of 30 g/day, urea improves hypo-osmolality by increasing renal free water excretion and decreasing urinary sodium. Even if only partially effective, it can allow reduction in water restriction.

Vasopressin receptor antagonists

Vasopressin receptor (VR) antagonists are a rational approach to the management of hyponatraemia mediated through the action of AVP. The recent development of non-peptide VR antagonists (the vaptans) brings this possibility closer. There are three VR subtypes: V1a, V1b and V2. The effects of AVP on renal free water excretion are mediated by the V2-R. V2-R antagonists are classified as either selective (V2-R specific) or non-selective (V2- and V1a antagonism). Both increase renal water excretion without a significant impact on renal electrolyte loss.

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Both are effective in the treatment of hyponatraemia associated with normal or increased plasma volume. The place of VR antagonists in the management of hyponatraemia is currently under development.

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KEY POINTS

- Hyponatraemia is associated with increased mortality and morbidity in patients with heart failure, liver disease and acute neurological syndromes.
- Hyponatraemia is often multifactorial.
- Clinical presentations are diverse, reflecting a number of influences, including the rate of development, scale, neurophysiological adaptive capacity and the influence of co-morbidities.
- Management requires a systematic approach based on clinical presentation.
- The regulation of sodium balance, water balance and circulating volume are linked and are best viewed as overlapping, co-ordinated neuro-humoral systems.
- Osmolar criteria for syndrome of inappropriate antidiuresis (SIAD) are met simply if urine is not maximally dilute in the face of coincident hyponatraemia.
- Many drugs used in everyday clinical practice cause SIAD and drug histories are an important part of the clinical assessment of patients presenting with hyponatraemia.

EDUCATION

SELF-ASSESSMENT QUESTIONS

1. Hyponatraemia is found in which one of the following percentages of non-selected emergency admissions to hospital in the UK?

A. 10%
B. 20%
C. 5%
D. 30%
E. 40%

2. The management of patients presenting with hyponatraemia should be primarily based on which one of the following?

A. The plasma sodium concentration.
B. The rate of onset of hyponatraemia.
C. The clinical status of the patient.
D. The blood pressure of the patient.
E. The presence or absence of co-morbidity.

3. Syndrome of inappropriate antidiuresis is characterised by which one of the following features?

A. Urine sodium concentration <20 mmol/l.
B. Plasma osmolality that exceeds urine osmolality.
C. Reduced plasma volume.
D. Urine sodium concentration >20 mmol/l.
E. Hypotension.

4. When correcting hyponatraemia, which one of the following statements best describes the desired rate of increase in plasma sodium?

A. Plasma sodium should be corrected to normal over 48 hours.
B. Plasma sodium should rise at no more than 8–10 mmol/l per 24 hours.
C. Plasma sodium should be brought rapidly to 125 mmol/l.
D. Plasma sodium should be corrected at a steady rate until it is in the normal range.
E. Plasma sodium should be corrected to normal as quickly as possible if hyponatraemia has developed rapidly.

5. Which one of the following statements best describes the use of hypertonic sodium chloride to correct hyponatraemia?

A. It should be used in all patients with symptomatic hyponatraemia.
B. It must be given at a constant rate to achieve normal sodium levels.
C. It must be used in a high-dependency setting with close clinical and biochemical monitoring.
D. It can only be used in patients with hypovolaemia.
E. Treatment should continue until normal plasma sodium concentration is achieved.

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