

Asymptomatic Hyponatraemia on the Acute Medical Unit

M Patel

Key Points

- Hyponatraemia is a common finding in asymptomatic patients presenting on the acute medical take.
- Establishing a cause for hyponatraemia requires assessment of the patient's volume status, which will also determine the treatment options.
- Rapid correction with hypertonic saline is only indicated for severe symptomatic hyponatraemia, and requires careful monitoring.

Abstract

Hyponatraemia is defined as a serum sodium concentration of 135 mmol/L or less. It is the most common electrolyte abnormality, and can be associated with significant morbidity and mortality.¹ There are numerous causes and a systematic approach to the initial investigation and management is required. Clinical assessment should start with evaluation of the patient's degree of hydration, with the measurements of serum and urine osmolality and urinary sodium concentration being the key biochemical investigations. A recent article in this journal highlighted the challenges associated with acute symptomatic hyponatraemia; this article concentrates on the more common scenario of the patient with asymptomatic hyponatraemia.

Keywords

Hyponatraemia, volume status, Antidiuretic Hormone, paired plasma and urine osmolality, urinary sodium.

Background

Sodium and water balance

The relationship between sodium balance and extracellular fluid (ECF) volume is complex, with the maintenance of normal blood volume and osmolality being essential for body function. Sodium balance determines both the ECF volume and blood pressure. Hormonal mechanisms also exist for controlling both serum osmolality and blood pressure. Through their stimulation of vasoconstriction, vasodilatation and alteration of blood volume, sodium absorption or secretion is promoted.

Antidiuretic hormone (ADH) is the main hormone involved in water balance, though renin, aldosterone, angiotensin and atrial natriuretic peptide also contribute (Figure 1). ECF osmolality is maintained between 275–295 mmol/kg and is

largely influenced by serum sodium concentration, as sodium salts are the most abundant solutes. Changes in sodium balance affect serum osmolality as the movement of water is passive and follows solutes. Hyponatremia is defined as a serum sodium concentration of 135 mmol/L or less.²⁻⁴

At steady state, water intake and water losses are matched. If losses exceed intake, thirst is stimulated and fluid intake increases. Renal water conservation is the first-line defense against water depletion, but this mechanism is insufficient in settings of significant dehydration and hypertonicity. Moreover, the stimulation of thirst is required to maintain homeostasis. It has been reported that the thirst mechanism may be reduced with advancing age.⁵⁻⁸

Hypothalamic osmoreceptors detect changes in serum osmolality and stimulate ADH secretion accordingly. ADH is rapidly released from the posterior pituitary gland in response to an increase in serum osmolality. It then activates renal processes which promote the reabsorption of water from the collecting ducts, resulting in a dilution of ECF with concentrated urine. Conversely, a decline in plasma osmolality will reduce ADH secretion, resulting in the production of dilute urine. ADH release is not impaired with aging, but ADH levels are increased for any given plasma osmolality level, indicating a failure of the normal responsiveness of the kidney to ADH.⁹

ADH release is also stimulated in response to carotid baroreceptors detecting hypotension. The retention of water takes priority over osmotic regulation in the severely dehydrated state.

Renin secretion from the kidney is increased during situations associated with reduced extracellular fluid volume or pressure, or reduced sodium concentrations in the renal filtrate. Renin then triggers the conversion of angiotensinogen to angiotensin I. Angiotensin I is converted by angiotensin-converting enzyme (ACE) to angiotensin II. Angiotensin II can then trigger vasoconstriction, aldosterone release from the adrenal cortex and ADH release. Aldosterone causes absorption of sodium at the distal renal tubule. Sodium retention promotes free water retention, helping to correct the hypovolaemic state.

Disorders of sodium balance can generally be attributed to a disturbance in thirst or water acquisition, ADH, aldosterone, or renal sodium transport.

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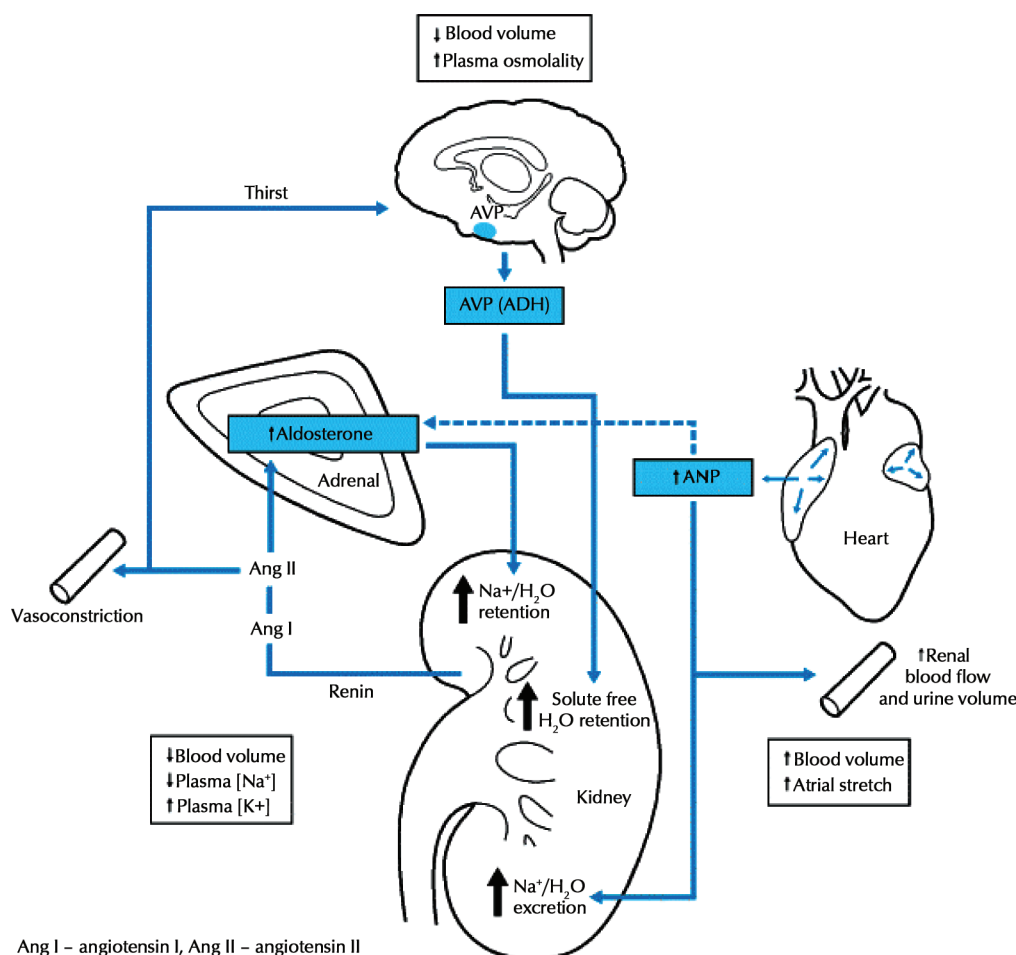


Figure 1. The integrated actions of ADH (antidiuretic hormone/arginine vasopressin (AVP)), aldosterone and atrial natriuretic peptide (ANP) in the control of salt and water balance. (from *Endocrinology, an Integrated Approach*, (2001, page 155), reproduced with permission from BIOS Scientific Publishers Limited).

Clinical Assessment

It is unusual for a patient to present to the admitting medical team with a known diagnosis of hyponatraemia. The more common scenario is when hyponatraemia is noted on the initial biochemistry profile, which is then phoned through to the admitting ward. There can be features in the patient history that may point to an electrolyte disturbance.

Clinical features will depend on the rate of development of hyponatraemia, as well as on the underlying cause. The presence of a relative water excess in hyponatraemia primarily affects brain function, as the intracellular movement of water results in a secondary swelling of neurones. Neurological symptoms tend to be observed with a measured concentration of less than 115–120 mmol/L and are on a progressive spectrum from nausea, malaise or headaches, through to confusion, seizures and coma.

When serum sodium concentration falls slowly, over a period of several days or weeks, the brain is able to compensate, through extrusion of solutes and fluid to the extracellular space. This reduces the flow of free water into the intracellular space, and symptoms are much milder for a given degree of hyponatremia.^{10,11} With a rapid decline in serum sodium, over a period of 24–48 hours,

this compensatory mechanism is overwhelmed and severe cerebral edema may develop, resulting in brainstem herniation and death.

History

The likely causes of hyponatraemia can be ascertained by taking a comprehensive history and considering if the patient is hypovolaemic, euvolaemic or hypervolaemic (Table 1).

Hyponatraemia can occur as a result of losing both body water and sodium together, such as in states associated with hypovolaemia. Volume depletion is suggested by symptoms such as diarrhoea, vomiting or acute blood loss, as well as by the use of diuretics. Remembering to ask about the patient's awareness of thirst can be helpful.

It is important to scrutinize the drug history fully, with attention also focussed on recently discontinued medications. Numerous drugs can cause the syndrome of inappropriate ADH secretion (SIADH) (Table 2), which is discussed in more detail later. Illicit drug use should be considered in younger patients. Methylenedioxymethamphetamine (ecstasy) induced hyponatremia occurs via several mechanisms; these include the induction of SIADH, the encouragement to drink large amounts of water to prevent unpleasant side effects of the drug, and

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Volume status	Urinary sodium Concentration	Causes
Hypovolaemic	Low	Non renal depletion (Gastro-intestinal, cutaneous or blood extracellular fluid loss)
	High	Renal depletion (salt-losing nephropathy, mineralocorticoid insufficiency, diuretics)
Euvolaemic	Low	Non renal depletion with hypotonic fluid replacement Syndrome of Inappropriate ADH (SIADH) with fluid restriction
	High	SIADH, glucocorticoid deficiency, diuretics
Hypervolaemic	Low	Reduced arterial blood volume (congestive heart failure, nephrosis, cirrhosis)
	High	Improvement in underlying disease, renal failure, diuretics

Table 1. Causes of hyponatraemia based on patient volume status & urinary sodium concentration.

- Anti-psychotics (phenothiazines)
- Anti-depressants (amitriptyline, fluoxetine, sertraline)
- Anticonvulsants (carbamazepine)
- Chemotherapeutic agents (cyclophosphamide, cisplatin, vincristine, vinblastine)
- Hallucinogenics (Methylenedioxymethamphetamine [ecstasy])
- Opiates
- Sulphonylureas (chlorpropamide)

Table 2. Drugs causing SIADH (syndrome of inappropriate ADH secretion).

the tendency among those intoxicated to be involved in vigorous physical activity that results in heavy sweating. Angiotensin-converting enzyme (ACE) inhibitors have also been associated with dilutional hyponatremia, accompanied by features of SIADH.¹²

With hypervolaemia, the presence of a relative excess of water to solute results in the dilution of sodium. It is important to glean features in the history that may point towards excessive fluid intake (psychogenic polydipsia, psychiatric disease) or increased water reabsorption (renal, cardiac or hepatic disease). It is highly unlikely that reduced dietary intake of sodium will cause hyponatraemia, as renal conservation of sodium is a highly efficient process in the absence of renal disease.

Examination

Neurological status, including measures of alertness and cognitive function should be assessed and regularly monitored. Acute severe hyponatremia can be associated with signs of brainstem herniation which include coma, a fixed, unilateral, dilated pupil; decorticate or decerebrate posturing; and respiratory arrest.

One of the key principles in determining a cause of hyponatraemia is to make an accurate assessment of the patient's volume status. Assessment for hypovolaemia can be difficult, as the classically described sunken eyes and reduced skin turgor are not often useful signs in adults. The presence of a tachycardia and postural hypotension are useful signs, but can be influenced by drugs. Hyperpigmentation can suggest adrenal insufficiency.

Signs of fluid overload are easier to identify, such as evidence of a raised jugular venous pressure, pulmonary crepitations, peripheral oedema or ascites. Patients who lack findings of hypovolemia or hypervolemia are considered to have *euvolemic* hyponatremia, which can be consistent with etiologies such as an exogenous free water load, hypothyroidism, cortisol deficiency, or SIADH.

Investigations

The possibility of blood sampling error should be considered, especially when the reported value does not seem consistent with the history or examination findings. It should be ensured that the sample was labeled from the correct patient and not obtained from a venous site proximal to an infusion of hypotonic saline or dextrose. Errors in laboratory measurement or reporting should be excluded and if an error is suspected, the serum sodium measurement should be repeated before therapeutic measures are initiated.

The diagnosis of pseudohyponatremia should also be considered. The larger relative concentration of lipids or proteins can artifactually reduce the measured sodium concentration. The use of ion specific electrodes to measure sodium rather than by flame photometry nowadays results in this phenomenon being reported less often. Serum glucose should also be measured, as hyperglycaemia can result in an osmotic shift of water from the intracellular to the extracellular fluid compartment, leading to a dilutional decrease in serum sodium.

Key investigations in hyponatraemia are the assessment of *paired* plasma and urinary osmolality and a urinary sodium measurement (Table 1). Thyroid function tests and a short synacthen test are also indicated, to exclude hypothyroidism or adrenal insufficiency respectively. Hyperkalemia may also suggest adrenal insufficiency. A urinary protein assessment is relevant if nephrotic syndrome is queried.

Osmolality

The plasma osmolality can be both calculated by formula (Figure 2) and be directly obtained by laboratory measurement. A discrepancy between the results of calculated and measured osmolalities obtained (>10 mol/

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- Calculated plasma osmolality: $2(\text{Na}^+ + \text{K}^+) + \text{Urea} + \text{Glucose}$
- Normal range: 275–295 mmol/kg
- (Na^+ = serum sodium concentration (mmol/L))
- (K^+ = serum potassium concentration (mmol/L))

Figure 2. Calculation of plasma osmolality.

kg) may indicate the presence of extra unmeasured solutes, such as toxins (ethanol, methanol and ethylene glycol) and the history may need to be reviewed.

Urinary sodium

With hypovolaemia, a renal cause for sodium loss would be suggested if measured urinary sodium exceeded 20 mmol/L. Examples include salt losing nephropathy or interstitial nephritis or Mineralocorticoid deficiency. Measured urinary sodium of less than 20 mmol/L would suggest an appropriate compensatory response to a non renal cause, such as gastrointestinal disease or excessive cutaneous fluid loss, as with burns or major trauma.

In the case of hypervolaemia, measured urinary sodium of less than 20 mmol/L would support diagnoses of excess water intake, cirrhosis, congestive cardiac failure or nephrotic syndrome. These states are associated with increased total body water but reduced effective arterial blood volume, leading to increased renal sodium reabsorption. Renal failure and diuretic use may also increase urinary sodium and confuse the clinical picture.

Syndrome of inappropriate ADH (SIADH)

SIADH is a diagnosis of exclusion, characterized by the continued release of ADH in the face of dilution of body fluids and increased extracellular volume. The urine is “inappropriately” concentrated when the body is trying to correct a state of hypotonicity. For a diagnosis of SIADH, there must be hyponatraemia with clinical euvoemia or hypervolaemia, as well as hypotonic plasma (osmolality <270 mmol/kg) with inappropriate urine osmolality (>100 mmol/kg). Renal, thyroid and adrenal function should also be normal. Common non-pharmacological causes of this disorder are summarized in Table 3. Aside from a review of the history for clues to a cause, a chest X-ray should be the first line radiological investigation where malignancy or respiratory diseases are suspected. It should be noted

that SIADH is commonly idiopathic with no clear underlying cause identified.

Urinary sodium will usually be inappropriately elevated (greater than 20 mmol/L) in SIADH, believed to be a result of hypervolaemia stimulating atrial stretch receptors, resulting in release of atrial natriuretic peptide.¹³

Treatment

The rate at which hyponatraemia should be treated will largely depend on the presence or absence of symptoms and their severity and whether the disorder is acute or chronic.^{14,15} Treatment of acute hyponatraemia was dealt with in the previous edition of this journal. This article will concentrate on the treatment of Chronic hyponatraemia.

Treatment of chronic hyponatraemia

The treatment of chronic asymptomatic hyponatremia should be conservative, i.e. fluid restriction in euvoemic or hypervolaemic states and normal saline administration in hypovolaemic cases (see later).

In asymptomatic patients in whom hyponatraemia has developed over more than 48 hours, the rapid correction of serum sodium is not indicated. Correction rates of 0.5 mmol/L per hour or less and magnitudes of correction of less than 12 mmol/L in the first 24 hours have been proposed,¹⁸ though there is no consensus on this.

Hypertonic saline (with or without a loop diuretic) may be appropriate in the treatment of severely symptomatic chronic hyponatremia. A slightly higher correction rate for sodium of 1–2 mmol/L per hour may be required in this setting, although chronic hyponatremia must be managed with extreme caution to prevent serum sodium levels from increasing too quickly. The rapid correction of hyponatraemia is associated with the rapid transfer of free water out of neurones. This can result in the osmotic demyelination syndrome of central pontine myelinolysis, which leads to irreversible brain damage^{3,19,20} and is associated with significant morbidity and mortality.²¹ The serum sodium should be checked at least 2–4 hourly and the corrective treatment regimen adjusted accordingly. Acute treatment should be stopped either when the patients' symptoms have cleared, serum sodium is above 120 mmol/L and a total magnitude of correction of greater than 20 mmol/L is reached. Slower acting therapies (fluid restriction, oral rehydration etc) can then be resumed as appropriate to the cause.

For hypovolaemic hyponatraemia, diuretics should be withheld and oral fluid intake should be encouraged

Neoplastic	Respiratory	Neurological
Small cell carcinoma of the lung	Pneumonia	Infection (meningitis, encephalitis, brain abscess)
Pancreatic carcinoma	Bronchiectasis	Vascular (haemorrhage, thrombosis, embolism)
Lymphoma, Hodgkin's disease	Lung abscess	Trauma (intracranial or subarachnoid haemorrhage, subdural haematoma)
Bladder carcinoma	Tuberculosis	

Table 3. Non-pharmacological causes of SIADH.

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where possible. Controlled intravenous fluid replacement with isotonic normal saline (0.9%) can be used. Cautious potassium replacement should be considered, as hypokalaemia can accompany hyponatraemia.

If it is believed that the diagnosis is hypovolaemic hyponatraemia but the patient appears euvolaemic, it is appropriate to initially treat with limited volume of isotonic saline and monitor for improvement in measured serum sodium and plasma osmolality. An increase in urinary sodium with minimal change in serum osmolality in response to isotonic saline administration would suggest that the underlying cause of hyponatraemia is more likely to be SIADH.²²

With hypervolaemic hyponatraemia, fluid restriction to 500 ml – 1 l/day for *all* fluids should be enforced. Controlled diuretic therapy may be indicated as well as more precise treatments for the underlying cause.

Treatment of SIADH

If SIADH is made as a diagnosis, any contributing drugs should be stopped where possible and other non pharmacological causes sought and treated where possible. Fluid restriction of *all* fluids to 500 ml – 1 l/day is indicated. Once the patient is clinically euvolemic, the drive to secrete ADH is reduced and the patient is able to excrete the excess free water.

If significant improvement in hyponatraemia has not occurred after 48 hours of fluid restriction alone, specialist or senior review should be sought and demeclocycline can be used. This drug promotes free water excretion by inducing nephrogenic diabetes insipidus, thus correcting the hyponatraemic state.²³

Other treatments for hyponatraemia

If glucocorticoid deficiency is suspected, glucocorticoid replacement with hydrocortisone should be initiated, ideally after blood is sent for diagnostic testing (e.g. random cortisol or short synacthen test). Thyroid replacement therapy can be deferred until biochemical confirmation of hypothyroidism is made, unless the patient is obviously myxoedematous.

The future

A key advance in the management of hyponatremia is through the development of a new class of drugs called aquaretics. By antagonizing the action of ADH at the level of its vascular and renal receptors, these agents can promote the excretion of free water without electrolyte loss.^{24,25} Early work has demonstrated their ability to normalize sodium levels safely in patients who have euvolemic or hypervolemic hyponatremia secondary to cirrhosis, congestive cardiac failure and SIADH.^{26,25,27}

Conclusions

Hyponatraemia is a significant clinical problem, with many causes. A clear understanding of its pathophysiology is needed to initiate safe and effective corrective treatment. The assessment of volume status is a key factor in management. When this is taken with measures of plasma osmolality and urinary sodium concentration, the appropriate treatment can then be instigated.

References

1. Arieff AI. Hyponatraemia, convulsions, respiratory arrest, and permanent brain damage after elective surgery in healthy women. *N Engl J Med* 1986; **314**: 1529–1535.
2. Palmer BF, Gates JR, Lader M. Causes and management of hyponatremia. *Ann Pharmacother* 2003; **37**: 1694–1702.
3. Fried LF, Palevsky PM. Hyponatremia and hypernatremia. *Med Clin North Am* 1997; **81**: 585–609.
4. Oh MS. Pathogenesis and diagnosis of hyponatremia. *Nephron* 2002; **92**(Suppl 1): 2–8.
5. Phillips PA, Bretherton M, Johnston CI, *et al.* Reduced osmotic thirst in healthy elderly men. *Am J Physiol* 1991; **261**: R166–R171.
6. Phillips PA, Johnston CI, Gray L. Disturbed fluid and electrolyte homeostasis following dehydration in elderly people. *Age Ageing* 1993; **22**: S26–S33.
7. Takamata A, Ito T, *et al.* Effect of an exercise-heat acclimation program on body fluid regulatory responses to dehydration in older men. *Am J Physiol* 1999; **277**: R1041–R1050.
8. Kugler JP, Hustead T. Hyponatraemia and hypernatraemia in the elderly. *Am Fam Physician* 2000; **61**: 3623–3630.
9. Beck LH. Changes in renal function with aging. *Clin Geriatr Med* 1998; **14**: 199–209.
10. Verbalis JG, Gullans SR. Hyponatraemia causes large sustained reduction in brain content of multiple organic solutes in rats. *Brain Res* 1991; **567**: 274–282.
11. Gullans SR, Verbalis JG. Control of brain volume during hyperosmolar and hypoosmolar conditions. *Annu Rev Med* 1993; **44**: 289–301.
12. Subramanian D, Ayus C. Case report: Severe symptomatic hyponatremia associated with lisinopril therapy. *Am Med Sci* 1992; **303**: 177–179.
13. Kamoi K, Ebe T, *et al.* Atrial natriuretic peptide in patients with the syndrome of inappropriate antidiuretic hormone secretion and with diabetes insipidus. *J Clin Endocrinol Metab* 1990; **70**: 1385–1390.
14. drogue' HJ, Madias NE. Hyponatremia. *N Engl J Med* 2000; **342**: 1581–1589.
15. Han DS, Cho BS. Therapeutic approach to hyponatremia. *Nephron* 2002; **92**(Suppl 1): 9–13.
16. Decaux G, Musch W, Soupart A. Hyponatremia in the intensive care: from diagnosis to treatment. *Acta Clin Belg* 2000; **55**: 68–78.
17. Decaux G, Soupart A. Treatment of symptomatic hyponatremia. *Am Med Sci* 2003; **326**: 25–30.
18. Sterns RH, Cappuccio JD, Silver SM, *et al.* Neurologic sequelae after treatment of severe hyponatraemia: a multicentre perspective. *J Am Soc Nephrol* 1994; **4**: 1522–1530.
19. Sterns RH, Cappuccio JD, Silver SM, *et al.* Neurologic sequelae after treatment of severe hyponatremia: multicenter perspective. *Am Soc Nephrol* 1994; **4**: 1522–1530.
20. Sterns RH. The treatment of hyponatremia: First, do no harm. *Am Med* 1990; **88**: 557–560.

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21. Sterns RH, Riggs JE, *et al.* Osmotic demyelination syndrome following correction of hyponatraemia. *N Engl J Med* 1986; **314**: 1535–1542.
22. Schwartz WB, Bennett S, *et al.* A syndrome of renal sodium loss and hyponatraemia probably resulting from inappropriate secretion of antidiuretic hormone. *Am J Med* 1957; **23**: 529–542.
23. Cherrill DA, Stote RM, Birge JR, *et al.* Demeclocycline treatment in the syndrome of inappropriate antidiuretic hormone secretion. *Ann Intern Med* 1975; **83**: 654–6.
24. Verbalis JG. Vasopressin V2 receptor antagonists. *Mol Endocrinol* 2002; **29**: 1–9.
25. Palm C, Reimann D, Gross P. The role of V2 vasopressin antagonists in hyponatremia. *Cardiovasc Res* 2001; **51**: 403–408.
26. Wong LL, Verbalis JG. Vasopressin V2 receptor antagonists. *Cardiovasc Res* 2001; **51**: 391–402.
27. Wong F, Blei AT, Blendis LM, *et al.* vasopressin receptor antagonist (VPA985) improves serum sodium concentration in patients with hyponatremia: multicenter, randomized, placebo-controlled trial. *Hepatology* 2003; **37**: 182–191.