Vasopressin-receptor antagonist therapy in patients with hyponatraemia

Hyponatraemia often complicates the treatment of underlying conditions in patients who are seriously ill. Arginine vasopressin receptor antagonists block the action of arginine vasopressin and correct sodium and water imbalance in patients with euvolaemic or hypervolaemic hyponatraemia.

Hyponatraemia is a common, potentially serious electrolyte disorder associated with a broad variety of underlying illnesses, surgical procedures, and drug treatments (Anderson et al, 1985; Wong and Verbalis, 2001; Palmer et al, 2003). A serum sodium (Na^+) concentration <135 mEq/litre may occur in up to 22% of hospitalized patients (Wong and Verbalis, 2001). Critically ill patients are at increased risk for hyponatraemia. A prospective study of 98 consecutive admissions to an intensive care unit identified hyponatraemia (serum Na^+ ≤134 mEq/litre) in 29 patients (30%) (DeVita et al, 1990).

The elderly are at increased risk for hyponatraemia because of age-related changes in renal anatomy and physiology (Miller, 2001; Tareen et al, 2005). In a large geriatric inpatient cohort, the prevalence of hyponatraemia (serum Na^+ <130 mEq/litre within 24 hours of hospital admission) was 3.5% (Terzian et al, 1994). In-hospital mortality was 16% among patients with hyponatraemia, compared with 8% among those admitted without hyponatraemia (Terzian et al, 1994).

Water balance is regulated by the thirst mechanism, the secretion of arginine vasopressin (AVP) by the posterior pituitary, and the kidney's response to AVP. Renal water excretion is under the direct control of AVP (Wong and Verbalis, 2002). Aquaporin-2 channels, which are located predominately in the apical plasma membrane and apical vesicles in the collecting duct principal cells and, to a lesser extent, in the connecting tubules, are the primary target for AVP regulation of water permeability at the level of the collecting duct (Nielsen et al, 1999). A diagnosis of hyponatraemia indicates an excess of water relative to solute in body fluids and represents the inability of the osmoregulatory system to function properly (Beck, 1998).

Euvolaemic hyponatraemia is the most common type of hyponatraemia in hospitalized patients (Anderson et al, 1985), and the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is the most frequent cause of euvolaemic hyponatraemia (Wong and Verbalis, 2001). In patients with SIADH, AVP is not regulated physiologically; hypo-osmolar conditions fail to suppress its secretion. Because the sensitivity of osmoreceptors increases with age, healthy elderly individuals may demonstrate hyponatraemia with features of SIADH (Baylis, 2003).

Patients with hypervolaemia who have advanced congestive heart failure (CHF) or cirrhosis with ascites frequently have hyponatraemia (Gines and Jimenez, 1996; Wong and Verbalis, 2002). Both underlying conditions are associated with a chronic elevation of AVP concentration and impaired free water excretion (Ferguson et al, 2003; Lee et al, 2003). Despite the presence of hypervolaemia and oedema, pronounced retention of both sodium and water occurs in an attempt to maintain effective arterial blood volume.

Treatment options for hyponatraemia have been limited. The mainstays of therapy include saline infusion for patients who have acute symptomatic hyponatraemia and fluid restriction for those with chronic asymptomatic or mildly symptomatic hyponatraemia (Adrogué and Madias, 2000). Current therapeutic options do not provide effective, well-tolerated treatment for chronic hyponatraemia unresponsive to fluid restriction, nor do they offer specific therapy directed at the AVP dysregulation and underlying hypo-osmolar hyponatraemia in many patients who have euvolaemia or hypervolaemia (Janicic and Verbalis, 2003).

Treatment options for hyponatraemia

Treatment of hyponatraemia necessitates an assessment of the disorder's severity and duration, the patient's symptoms, and the risk factors for serious neurological complications (Han and Cho, 2002; Tareen et al, 2005). Pharmacological therapy has been suboptimal (Janicic and Verbalis, 2003) and is hampered by a lack of consensus, particularly regarding symptomatic patients (Adrogué and Madias, 2000).

Because patients with hyponatraemia may be asymptomatic or have only mild symptoms, the disorder may remain unrecognized and therefore untreated (Goh, 2004). Early symptoms of hyponatraemia may be non-specific (e.g. headache, lethargy) (Goh, 2004); other

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clinical manifestations include anorexia, confusion, and muscle cramps, followed by nausea, vomiting, and progressive neurological abnormalities (Albanese et al, 2001). A careful assessment of the neurological status is required for patients without overt symptoms. In elderly patients, subtle findings such as loss of attention may be one of the earliest signs of hyponatraemia and a marker for more serious consequences (Miller, 2001). For example, in a study that included 122 patients with asymptomatic chronic hyponatraemia (serum Na^+ <128 mEq/litre) and 244 matched control subjects (mean age 72 and 71 years, respectively), attention deficits and gait disturbances may have contributed to the significantly higher prevalence of falls among the patients with hyponatraemia (21.3% *vs* 5.3%; $P<0.001$) (Renneboog et al, 2006).

The rate of serum Na^+ correction is critically important. For example, an excessively slow correction in patients with acute symptomatic hyponatraemia is associated with increased morbidity and mortality as a result of cerebral oedema (Arieff, 2001; Rabinstein and Wijdicks, 2003), whereas correction that is too rapid in patients with chronic hyponatraemia is associated with central pontine myelinolysis (Sterns et al, 1986; Sterns, 1991; Lampl and Yazdi, 2002). The duration of hyponatraemia may be difficult to establish (Decaux et al, 2000). Acute symptomatic hyponatraemia is generally hospital acquired, frequently developing in the postoperative period; exceptions include acute hyponatraemia associated with thiazide administration, polydipsia, or extreme exercise, which occur outside the hospital. Most cases of hyponatraemia in outpatients are subacute or chronic (Mulloy and Caruana, 1995).

Patients with acute symptomatic hyponatraemia and clinical euvolaemia require prompt, controlled correction with hypertonic (3%) saline – often combined with furosemide to limit volume expansion (Adrogué and Madias, 2000; Palmer et al, 2003). A correction rate greater than 12 mEq/litre per day or 0.5 mEq/litre per hour should be avoided (Mulloy and Caruana, 1995). Treatment should be stopped once neurological symptoms abate; immediate normalization of serum Na^+ is usually safe but rarely necessary (Decaux and Soupart, 2003). In most patients, serum Na^+ between 125 and 130 mEq/litre is sufficient to reverse the major neurological complications of hyponatraemia (Miller, 2001). Additional therapy is more conservative and includes fluid restriction as well as treatment of the underlying disorder (Mulloy and Caruana, 1995).

Patients with clinical hypovolaemia of any severity should be given isotonic saline at a rate appropriate for the estimated volume depletion (Janicic and Verbalis, 2003). Saline infusion should be supplemented with potassium chloride if diuretic use is confirmed or suspected. Patients with hypervolaemic hyponatraemia rarely require immediate therapy to increase plasma osmolality. Loop diuretic therapy is preferred for patients with oedematous conditions, and treatment with furosemide and an angiotensin converting-enzyme inhibitor is effective in patients who have hyponatraemia with CHF (Sterns, 1991).

Patients with chronic hyponatraemia (i.e. >48 hours' duration) usually have minimal neurological symptoms, although the disorder may manifest with an acute symptomatic episode (Janicic and Verbalis, 2003). The correction of serum Na^+ in patients with chronic hyponatraemia is not usually urgent. Nevertheless, the treatment regimens available have been limited. Fluid restriction (to <800 ml/day) has been the mainstay of treatment for patients with persistent hyponatraemia associated with SIADH or oedematous conditions (Adrogué and Madias, 2000).

The limited treatment options in patients with hyponatraemia, particularly those with AVP-induced antidiuresis and volume expansion, have prompted the search for alternative therapy. The recent development of AVP-receptor antagonists, which act directly on the renal tubules to block the antidiuretic effects of AVP, could be an alternative for patients with euvolaemic or hypervolaemic hyponatraemia.

AVP-receptor antagonists for the treatment of hyponatraemia

AVP is a peptide secreted by the posterior pituitary that regulates body fluid homeostasis (Thibonnier et al, 2001). Sites of AVP action include V1A receptors in vascular smooth muscle that mediate vasoconstriction, thereby regulating blood pressure, and V2 receptors in the renal distal tubule and collecting ducts that mediate free water reabsorption, thereby regulating body fluid osmolality (Wong and Verbalis, 2001). Conivaptan, which blocks V1A and V2 receptors, is the first AVP-receptor antagonist approved for the treatment of euvolaemic and hypervolaemic hyponatraemia in hospitalized patients. Two other V2-receptor antagonists (lixivaptan and tolvaptan) are under investigation.

The V2-receptor antagonist lixivaptan (VPA-985) was evaluated primarily in hospitalized patients with hyponatraemia (serum Na^+ 115–132 mEq/litre) and oedematous disorders, usually cirrhosis with ascites, in two randomized multicentre trials (Gerbes et al, 2003; Wong et al, 2003). In each 7-day study, oral lixivaptan – combined with usual therapy including diuretics and fluid restriction – increased free water clearance (FWC) and serum Na^+ without significant changes in electrolyte excretion, systemic haemodynamics, or renal function.

Tolvaptan, a V2-receptor antagonist, was evaluated in patients with systemic congestion secondary to CHF in two double-blind, multicentre trials. In the first study, 254 outpatients with mild congestive symptoms were randomly assigned to receive oral therapy with tolvaptan (30, 45, or 60 mg) or placebo once daily for 25 days (Gheorghiade et al, 2003). All patients were receiving oral furosemide at a stable dose as well as

standard therapy for CHF. Among the 70 patients with hyponatraemia at baseline (serum Na^+ <136 mEq/litre), 82% of those given tolvaptan, had a normal serum Na^+ at the end of treatment *vs* 40% of patients given placebo. Normalization of serum Na^+ occurred on the first day of treatment in 80% of tolvaptan recipients.

In the second trial, 319 patients hospitalized for worsening CHF despite undergoing standard therapy were given tolvaptan (30, 60, or 90 mg) or placebo once daily (Gheorghiade et al, 2004). Tolvaptan was more effective than placebo in correcting serum Na^+ in the 68 patients with hyponatraemia at baseline (serum Na^+ <136 mEq/litre).

The effect of tolvaptan on the normalization of serum Na^+ (≥135 mEq/litre or an increase of ≥10% from baseline) was also evaluated in a multicentre, open-label, dose-titration study (Gheorghiade et al, 2006). Twenty-eight patients with euvolaemic or hypervolaemic hyponatraemia were randomly assigned to receive tolvaptan (n=17) or undergo fluid restriction and receive placebo (n=11). By the last inpatient visit or day 12, whichever came first, significantly more patients who received tolvaptan than those who underwent fluid restriction demonstrated a normalization of serum Na^+ (11 *vs* 3, P=0.049).

The efficacy of conivaptan, a V1A/V2-receptor antagonist, was evaluated in patients with euvolaemic or hypervolaemic hyponatraemia (serum Na^+ 115 to <130 mEq/litre). In a multicentre, randomized, double-blind, phase III trial (Verbalis and Smith, 2004), 84 patients were randomly assigned to receive placebo or conivaptan 40 or 80 mg/day in a 4-day continuous infusion (following 30-minute infusion of a 20 mg loading dose on day 1). The mean change from baseline in serum Na^+ at day 4 was 6.8 mEq/litre with conivaptan 40 mg/day and 9.0 mEq/litre with conivaptan 80 mg/day, compared with 2.0 mEq/litre with placebo. In a separate analysis of the subset of patients with euvolaemic hyponatraemia (n=56), the mean change in serum Na^+ from baseline by the end of treatment was 6.1 mEq/litre with conivaptan 40 mg/day, compared with 2.8 mEq/litre with placebo (P<0.05) (Verbalis et al, 2006). Conivaptan was well tolerated; the most common adverse events included injection-site reactions, postural hypotension and thirst.

In two supportive phase III oral-dosing studies, conivaptan was effective in the correction of serum Na^+ when administered at 40 or 80 mg/day for 5 days in patients with euvolaemic or hypervolaemic hyponatraemia (Gross and Smith, 2004; Ghali et al, 2006). Conivaptan, however, is a substrate and inhibitor of the cytochrome P450 isozyme 3A4; based on these findings, only the intravenous formulation of conivaptan has been approved for the treatment of euvolaemic and hypervolaemic hyponatraemia in hospitalized patients.

Determining the appropriate patients for AVP-receptor antagonist therapy

Hyponatraemia secondary to AVP dysregulation can occur in a variety of patient populations, including the elderly, patients with SIADH, CHF, cirrhosis, or hypothyroidism, postoperative patients, and compulsive water drinkers. Owing to the difference in mechanisms of action among the AVP-receptor antagonists, however, not all agents may be appropriate in these patients. In addition, AVP-receptor antagonists are contraindicated in patients who have hypovolaemic hyponatraemia.

Elderly patients

Age-related changes in renal anatomy and physiology increase the risk of hyponatraemia in the elderly (Miller, 2001; Tareen et al, 2005). Renal changes that accompany normal ageing include decreased numbers of glomeruli, a decline in renal blood flow, and decreased glomerular filtration rate (Miller, 2001). Elderly individuals have a limited ability to tolerate water deprivation or to handle large water loads (Beck, 1998). Because of their decreased ability to dilute the urine and excrete a water load, the elderly are at increased risk of water retention and hyponatraemia when increasing fluid intake (Miller, 2001).

Each person's maximal urinary concentrating ability also decreases with ageing (Beck, 1998). For any given plasma osmolality, the level of circulating AVP is higher in older individuals than in younger persons. In the elderly, the presence of elevated AVP concentration, coupled with an age-related reduction in maximal urinary concentrating ability, reflects the failure of normal renal responses to AVP.

In addition, elderly patients take more medications than younger ones. Many of these drugs, including nicotine, high-dose morphine, adrenaline and non-steroidal anti-inflammatory drugs, can increase AVP secretion or the renal tubular response to circulating AVP (Tareen et al, 2005). Elderly patients with hypertension – particularly women – given thiazide diuretics are at increased risk for euvolaemic hyponatraemia, which usually occurs shortly after the administration of antihypertensive therapy, especially if there is an increased intake of hypotonic fluids (Mulloy and Caruana, 1995).

SIADH

AVP-receptor antagonist therapy may be appropriate for patients with confirmed euvolaemic hyponatraemia associated with SIADH (Verbalis, 2002). Although SIADH is primarily a diagnosis of exclusion, the cardinal features recognized by Bartter and Schwartz include hyponatraemia with hypo-osmolality of serum and extracellular fluid, continued renal excretion of sodium, absence of clinical evidence of volume depletion, urine less than maximally dilute, and normal renal and adrenal function (Bartter and Schwartz, 1967). Water retention with secondary natriuresis underlies the pathophysiology of

hyponatraemia in SIADH (Robinson, 1985). Patients with SIADH could benefit from AVP-receptor antagonist therapy regardless of the underlying etiology of their disorder – either ectopic production of AVP (as in malignant disease or pulmonary infection) or inappropriate AVP release from the pituitary (as in CNS disorders or drug-induced SIADH) (*Table 1*).

SIADH is treated as a chronic disorder when its underlying cause is unknown or cannot be treated effectively (Kinzie, 1987). In patients with SIADH resulting from cancer refractory to treatment, for example, fluid restriction has been the mainstay of long-term treatment (Miller, 2001). AVP-receptor antagonist therapy may be an effective alternative for treating hyponatraemia, as fluid restriction is difficult to maintain for prolonged periods and few of the pharmacological options available allow greater fluid intake (Kinzie, 1987).

Table 1. Aetiology of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH)

Ectopic production of antidiuretic hormone (ADH)	Malignant disease	Oat-cell carcinoma of lung
		Duodenal carcinoma
		Pancreatic carcinoma
		Hodgkin's lymphoma
		Lymphosarcoma
		Thymoma
	Non-malignant disease	Tuberculosis
		Staphylococcal pneumonia
		Lung abscess
Inappropriate release of ADH from neurohypophysis	CNS disorders	Skull fracture
		Subdural haematoma
		Subarachnoid haemorrhage
		Cerebral vascular thrombosis
		Hydrocephalus
		Cerebral atrophy
	Drug-induced SIADH	Chlorpropamide
		Cyclophosphamide
		Vincristine
		Cisplatin
		Vinblastine-bleomycin
		Tricyclic antidepressant agents
		Antipsychotic agents
		Selective serotonin-reuptake inhibitors
		General anaesthetics
		Narcotics
		Barbiturates
	Other	Surgical stress
		Pain
		Acute psychosis

Adapted from Kinzie (1987)

Drugs may cause hyponatraemia with characteristics of SIADH by increasing AVP release or enhancing its renal effects (Mulloy and Caruana, 1995; Miller, 2001). Commonly used drugs that have been associated with hyponatraemia include antipsychotic agents, antidepressants, and anticonvulsants. The newer selective serotonin-reuptake inhibitors can induce SIADH and hyponatraemia, especially in the elderly (Mulloy and Caruana, 1995). Drug-induced SIADH is a potential indication for AVP-receptor antagonists, as some patients may be unable to discontinue a needed medication (Verbalis, 2002).

Hypothyroidism

Hyponatraemia in hypothyroidism is associated with increased total body sodium, a diminished ability to excrete free water, failure to achieve maximum urine dilution, and delayed excretion of water load (Hanna and Scanlon, 1997). These physiological changes are accompanied by an increased plasma AVP level, which is not suppressed normally after ingestion of water. Although thyroid replacement is primary, titrated doses of AVP-receptor antagonists may prove effective for controlled free-water excretion in patients who have hypothyroidism with symptomatic or refractory hyponatraemia (Hanna and Scanlon, 1997; Verbalis, 2002). In addition, because hypothyroidism is more prevalent in the elderly, elderly patients with euvolaemic hyponatraemia should be evaluated for thyroid abnormalities (Tareen et al, 2005).

Surgical patients

Surgical patients usually have elevated AVP secretion for several days during the postoperative period (Mulloy and Caruana, 1995). Potential causes include decreased effective arterial blood volume, pain and stress, hypoxaemia, and drug administration (Rossi and Cadnapaphornchai, 1987). Postoperative hyponatraemia with acute hyponatraemic encephalopathy may develop if surgical treatment includes intravenous administration of large volumes of hypotonic fluids (Arieff, 1986).

The standard therapy for patients with acute symptomatic hyponatraemia has been intravenous administration of hypertonic saline to increase serum Na^+ and prevent neurological complications (Wong and Verbalis, 2001). As experience with AVP-receptor antagonists grows, the use of these agents for controlled but prompt serum Na^+ correction may provide an alternative to infusion of hypertonic saline in patients who demonstrate acute symptomatic hyponatraemia after surgery (Arieff, 2001).

Compulsive water drinkers

Hyponatraemia in psychotic patients may be indistinguishable from that in patients with SIADH, or it may be associated with appropriate urinary dilution and

compulsive water drinking (Rossi and Cadnapaphornchai, 1987). Usually, symptoms in extreme polydipsia are limited to marked polyuria, however, the disorder is occasionally associated with severe symptomatic hyponatraemia (Mulloy and Caruana, 1995). The underlying cause may be alterations in the regulation of AVP release or abnormalities in thirst perception (Miller, 2001).

In some patients suffering from compulsive water drinking, hyponatraemia spontaneously resolves after diuresis (Verbalis, 2003). When neurological symptoms are severe and urine output is <300 ml/h, infusion of hypertonic saline has been the usual approach (Sterns, 1991). AVP-receptor antagonist therapy may be an alternative that provides prompt and controlled correction of serum Na^+ in this patient population.

Congestive heart failure

Treatment with AVP-receptor antagonists may be useful for patients with confirmed hypervolaemic hyponatraemia associated with advanced CHF (Verbalis, 2002). Plasma AVP concentration is chronically elevated in patients with heart failure, particularly those with advanced disease and hyponatraemia (Lee et al, 2003). The impairment in free water excretion caused by chronic AVP elevation could increase congestive symptoms and thereby negatively affect patient outcomes (Rossi and Cadnapaphornchai, 1987). Hyponatraemia has been established as an independent predictor of death in patients hospitalized because of decompensated CHF (Brophy et al, 1994; Chin and Goldman, 1996).

Conventional diuretic therapy (administration of a loop diuretic) often fails to correct hyponatraemia in patients with CHF. Moreover, diuretic treatment activates neurohormonal systems – including the renin-angiotensin-aldosterone system – a process that further stimulates release of AVP (Lee et al, 2003). Therefore, diuretic therapy fails to address the elevated AVP concentration associated with CHF (Burrell et al, 2000; Wong and Verbalis, 2001). A reversal of the AVP-induced impairment in free water excretion through the administration of an AVP-receptor antagonist could correct hyponatraemia in patients with CHF. Antagonism of AVP effects at the renal V2 receptor produces aquaresis – enhanced FWC without loss of electrolytes – and therefore would treat hyponatraemia directly.

Cirrhosis

The treatment of hyponatraemia in patients with cirrhosis and ascites has not included any effective therapeutic options directed at impaired renal water excretion and elevated plasma AVP concentrations (Gines and Jimenez, 1996). Because hypo-osmolar hyponatraemia in these patients is accompanied by sodium retention, treatment with hypertonic saline is not recommended, as it may cause further expansion of extracellular fluid volume with worsening ascites and oedema.

Patients with advanced cirrhosis are often haemodynamically unstable, with reduced systemic blood pressure and renal dysfunction (Ferguson et al, 2003). Because administration of AVP-receptor antagonists may further reduce plasma volume, careful attention to systemic haemodynamics and renal function during treatment is necessary. Among the three AVP-receptor antagonists, only lixivaptan has been shown to improve serum Na^+ in patients with cirrhosis; additional studies are needed to determine the role of tolvaptan in this setting. Conivaptan should be used with caution in this patient population. The potential benefits include liberalizing fluid restriction and reducing morbidity associated with hyponatraemia (Verbalis, 2002).

Conclusions

Hyponatraemia occurs in a broad variety of patients, including those with cancer, CNS disorders and psychiatric illness, and patients undergoing surgery. A common disorder in hospitalized patients, hyponatraemia is associated with increased morbidity and mortality, particularly among those seriously ill and the elderly. Treatment options have been limited. AVP-receptor antagonists are a new pharmacological option that provides prompt but controlled correction of serum Na^+ in patients with euvolaemic or hypervolaemic hyponatraemia. Treatment with AVP-receptor antagonists could enhance FWC in states of AVP excess, regardless of the cause of AVP

KEY POINTS

- Hyponatraemia secondary to arginine vasopressin (AVP) dysregulation can occur in the elderly, patients with syndrome of inappropriate secretion of antidiuretic hormone (SIADH), congestive heart failure, cirrhosis, or hypothyroidism, postoperative patients, and compulsive water drinkers.
- Elderly individuals may lack normal renal responses to AVP owing to elevated AVP concentrations and an age-related reduction in maximal urinary concentrating ability.
- Patients with drug-induced SIADH who cannot discontinue the medication may benefit from AVP-receptor antagonist therapy.
- AVP-receptor antagonists have been shown to provide prompt but controlled correction of euvolaemic and hypervolaemic hyponatraemia.
- AVP-receptor antagonists promote aquaresis – enhanced free water clearance without loss of electrolytes – and can therefore directly treat hyponatraemia.

hypersecretion, by blocking the action of AVP at renal V2 receptors (Wong and Verbalis, 2001). For example, patients with euvolaemic hyponatraemia caused by SIADH could undergo treatment regardless of the underlying aetiology of their disorder. In patients with hypervolaemic hyponatraemia associated with oedematous conditions, antagonism of AVP's effects at the renal V2 receptor could reverse impaired excretion of free water without inducing a solute diuresis.

Continued research of this new drug class in various patient populations should further define the role of the AVP-receptor antagonists in the treatment of symptomatic hyponatraemia. **BJHM**

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