NEW APPROACHES TO HYPONATRAEMIA: THE VAPTANS

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ABSTRACT

The vaptans represent a new class of drug indicated for the treatment of hyponatraemia due to heart failure, cirrhosis, and the syndrome of inappropriate anti-diuretic hormone secretion (SIADH). The review critically considers the evidence basis, which supports the use of the vaptans in clinical practice.

Keywords: Hyponatraemia, Tolvaptan, Conivaptan, SIADH, Heart Failure

INTRODUCTION

Hyponatraemia is the most common electrolyte abnormality encountered in clinical practice. The incidence of hyponatraemia (defined as a serum sodium level of <135 mmol/L), in hospitalized patients is estimated at 15-20%. Hyponatraemia affects up to 18% of nursing home residents and 8% of aged matched non-nursing home patients [1].

Based on clinical and laboratory analyses, hyponatraemia can be classified into three categories: hypovolaemic (decreased volume), hypervolaemic (with venous oedema), and euvolaemic. The management of hyponatraemia depends on the underlying cause, which is defined within these three categories.

The symptomatology mainly includes neurological manifestations characterised by seizures, coma, or death due to brainstem herniation. In addition, it has been noted in recent years that uncertain gait, falls, fractures, and osteoporosis are also associated with hyponatraemia [2].

Severe hyponatraemia (<125 mmol/L) has a high mortality rate; for instance, when the serum sodium level is less than 105 mmol/L, the mortality is over 50%. In patients with acute ST-elevation myocardial infarction, the

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The presence of hyponatraemia on admission or early development of hyponatraemia is an independent predictor of 30-day mortality, and the prognosis worsens with the severity of hyponatraemia [3].

Traditionally, hyponatraemia was difficult to treat due to a lack of disease modifying drugs available to raise the serum sodium concentration. Until recently treatment was based on stopping offending agents, fluid restriction, and in severe cases, using hypertonic saline solutions. However, mild and moderate symptoms of hyponatraemia can now be managed with the controlled use of anti-diuretic hormone (ADH) antagonists; a new class of drug referred to as the vaptans. This review critically considers the role of the vaptans in the management of hyponatraemia.

**Physiology and Pharmacology**

ADH, also known as vasopressin, plays a central role in regulating body fluid homeostasis, serum osmolality, and vascular tone. In response to elevated serum osmolality, vasopressin acts on the renal tubules increasing water re-absorption, which decreases serum sodium.

Despite a crucial role in body fluid homeostasis, elevated vasopressin levels can also be pathological in conditions such as congestive heart failure, liver cirrhosis and SIADH. The elevated vasopressin levels result in renal water retention and hyponatraemia, which is associated with excess morbidity and mortality.

Vasopressin-receptor antagonists represent a new drug class of small molecules that competitively inhibit one or more vasopressin receptors. There are three vasopressin receptors in humans, $V_{1a}$, $V_{1b}$ and $V_2$. Selective $V_2$- and combined $V_{1a}/V_2$-receptor antagonists have been developed for the treatment of hyponatraemia resulting from congestive heart failure, liver cirrhosis and SIADH. Two non-peptide vasopressin-receptor antagonists, conivaptan and tolvaptan, have recently been approved by American and European drug authorities for clinical use [4].

Conivaptan is administered intravenously and tolvaptan is taken orally. Both agents produce highly effective and safe aquaretics to increase serum sodium levels. Tolvaptan is an inhibitor and substrate of P-glycoprotein (P-gp) and is metabolised by cytochrome CYP3A4 in the liver. The absolute bioavailability of tolvaptan is unknown but at least 40% of each dose is absorbed with peak concentrations occurring 2- to 4- hours after each dose. Food has no effect on bioavailability. The volume of distribution of tolvaptan is 3L/kg with 99% of the drug bound to plasma protein. Tolvaptan has a half-life of 12 hours and is excreted through faecal elimination [5].

The vaptans are indicated for the treatment of hyponatraemia associated with SIADH, cirrhosis and heart failure. In hypovolemic hyponatraemia their use is contraindicated [6].
EFFICACY

The vaptans appear to be effective in the acute exacerbations of heart failure that need hospitalisation. In the short-term tolvaptan relieves acute congestive symptoms and improves mortality[9]. The favorable short-term effects are ascribed to selective V_2 receptor blocking, while the unopposed stimulation of V_{1A} may give an explanation for the lack of long-term benefit.

Evidence in support of this comes from the Study of Ascending Levels of Tolvaptan 1 and 2 (SALT-1 and -2) trials [7, 8]. SALT-1 and -2 were two identical, randomised, double-blind, placebo-controlled, multicentre trials, which included patients with hypervolaemic or euvolaemic hyponatraemia (serum sodium <135 mmol/L) associated with heart failure, cirrhosis or SIADH. In both trials, patients receiving (in addition to standard medical treatment) tolvaptan 15-60 mg once daily (titrated according to response) for up to 30 days (n = 95 and 118) experienced significantly greater improvements than those receiving placebo (n = 89 and 114) for the co-primary endpoints of the change in average daily area under the curve for the serum sodium level from baseline to day 4 and from baseline to day 30. This beneficial effect of tolvaptan on serum sodium levels in SALT-1 and -2 was observed in patients with mild (serum sodium <135 mmol/L) and in those with marked (serum sodium <130 mmol/L) hyponatraemia at baseline.

The Efficacy of Vasopressin Antagonism in hEart failuRE Outcome Study With Tolvaptan (EVEREST) was a program of 3 pivotal trials [9]. These were designed to evaluate the effects of tolvaptan on symptoms and fluid balance during the inpatient period (Trials A and B), as well as the long-term effects of the drug on morbidity and mortality, in patients hospitalised with acutely decompensated heart failure. A total of 4,133 patients were randomised to tolvaptan (n = 2,072) or matching placebo (n = 2,061). Baseline characteristics were similar between the 2 groups, including the use of standard medical therapies. At 7 days or hospital discharge, change in body weight was significantly better in patients randomised to tolvaptan, but there was no difference in global clinical status between the 2 groups. However, a larger percentage of patients reported a beneficial change in dyspnoea and in oedema scoring. EVEREST found that oral tolvaptan on top of standard treatment for heart failure in hospitalised patients facilitates management of volume overload with the following observations noted: early and sustained weight reduction; improvement in dyspnoea and oedema; no effect on clinical status; normalisation of sodium; and maintenance of renal function. Whilst tolvaptan achieved short-term symptom benefit, long-term treatment did not have an effect on mortality or morbidity.

There are no studies comparing conivaptan with tolvaptan.
SAFETY

Tolvaptan should be initiated in a hospital setting because careful monitoring of fluid balance is recommended.

Data from phase III studies including over 5,000 patients have demonstrated that tolvaptan is a safe and well tolerated vasopressin receptor antagonist, whose long-term use is not associated with adverse outcomes. Side effects consist of thirst (16%), dry mouth (13%), polyuria (11%), asthenia (9%), constipation (7%), hyperglycaemia (6%), anorexia (4%), and pyrexia (4%). Less frequent (<1%) adverse effects include pollakiuria, and mild hypernatraemia. In patients with cirrhosis, gastrointestinal bleeding occurred more with tolvaptan (10%) than placebo (2%) [10].

A systematic review and meta-analysis of 15 randomised controlled trials on tolvaptan found that adverse events were not significantly increased compared to placebo. Whilst there was a rapid rate of sodium correction there were no reports of significant hypernatraemia or osmotic demyelination syndrome [11].

Tolvaptan inhibits digoxin excretion causing a steady-state increase in serum digoxin concentrations [12]. Tolvaptan does not alter steady-state amiodarone or desethylamiodarone concentrations and the co-administration of tolvaptan and amiodarone is safe [13].

ROLE IN CLINICAL PRACTICE

The vaptans represent a breakthrough in the therapy of hyponatraemia as they directly combat elevated vasopressin levels associated with SIADH, congestive heart failure, and cirrhosis of the liver.

Tolvaptan has a convincing evidence basis to support its use in acutely decompensated heart failure. However, its long-term effects in heart failure are controversial and need to be determined; prolonged use of tolvaptan leads to increased endogenous levels of vasopressin and perhaps over-stimulation of V1A receptors. Theoretically this activation could lead to increased afterload and cardiac myocyte fibrosis, causing progression of chronic heart failure. Further research on the effects of long-term use of tolvaptan in chronic heart failure is warranted [9].

There is some evidence to suggest tolvaptan may have a role in the treatment of autosomal dominant polycystic kidney disease (ADPKD) as tolvaptan has been shown to inhibit the development of ADPKD in mice [14]. The postulated mechanism is through inhibition of cyclic adenosine 3,5-monophosphate secretion, which is intra-cellular signal for renal cyst development. A phase III, placebo-controlled, double-blind study in 18- to 50 year-old patients with ADPKD and preserved renal function has been initiated and will determine whether tolvaptan is effective in slowing down the progression of this disease.
The cost-effectiveness of tolvaptan remains a contentious issue. Whilst it is clear that tolvaptan has a role in acutely correcting hyponatraemia, the economic data produced by the manufacturer does not take into account the fact that hyponatraemia often recurs in patients on cessation of the drug and there may be a number of patients requiring the drug long-term; paradoxically, there remains a lack of data demonstrating sustained efficacy. There may be a place in therapy for tolvaptan for a sub-group of elderly patients being treated concomitantly with anti-depressants or antipsychotic medication who develop iatrogenic SIADH. If the psychiatric symptoms are well controlled on these medications but SIADH develops then tolvaptan would be indicated.\textsuperscript{[15]}

CONCLUSION

The realisation that excessive vasopressin secretion is central in the pathophysiology of hyponatraemia in heart failure, cirrhosis, and SIADH, has led to the development of the vaptans. There is a substantial evidence basis to support their use for these conditions in the short term with a desirable efficacy to tolerability ratio. Long-term data on sustained efficacy and cost-effectiveness is needed if the vaptans are to become part of regular prescribing practice.

REFERENCES


