THE USE OF VAPTANS IN HYPONATRAEMIA

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ABSTRACT

Hyponatraemia is the most common electrolyte disorder in clinical practice. It is associated with increased morbidity, mortality, and length of hospital stay, and therefore represents a clinical, economic, and social burden for healthcare costs and caregivers. Acute and severe hyponatraemia is associated with severe neurological alterations that may lead to cerebral oedema and death. Even mild chronic hyponatraemia has been associated with neurological and extraneurological disorders, such as gait disturbances, attention deficit, increased risk of bone loss, falls, and fractures. These aspects appear relevant particularly in the elderly. Furthermore, an overly rapid correction of hyponatraemia may cause osmotic demyelination, thus making it necessary to define safe treatment strategies. In the last few years, the availability of new drugs, i.e. the vasopressin receptor antagonists or vaptans, has improved the therapeutic choices for the treatment of hyponatraemia. This review summarises the main aspects regarding the use of these drugs, in particular tolvaptan and conivaptan, which are the only vaptans currently available in clinical practice.

Keywords: Hyponatraemia, vasopressin receptor antagonists, vaptans, tolvaptan, conivaptan.

INTRODUCTION

Hyponatraemia is an electrolyte disorder defined as a serum sodium concentration ([Na+]) <136 mmol/L and represents a very important clinical and economic issue. Firstly because it is a very frequent alteration; in fact, it is the most common electrolyte imbalance in hospitalised patients, with a prevalence of mild forms ([Na+] 130-135 mmol/L) in about 20% of patients, and of moderate-to-severe forms ([Na+] <130 mmol/L) in about 7% of patients.[1,2] It is well known that acute severe hyponatraemia represents a life-threatening condition, causing brain oedema and severe neurological signs and symptoms.[3] However, in the last few years, new evidence has demonstrated that mild and chronic hyponatraemia, traditionally defined as an asymptomatic condition, may also have important clinical consequences such as attention deficits, gait instability, falls, osteoporosis, and increased risk of fractures.[4-8]

The association between hyponatraemia and increased mortality has been demonstrated in numerous conditions, such as myocardial infarction (MI),[9] heart failure (HF),[10] cirrhosis,[11] pulmonary diseases,[12] cancer,[9] in the elderly[13] and in intensive care patients.[14] Recently, in a comprehensive meta-analysis, we confirmed that hyponatraemia is a negative prognostic factor across a large series of hospitalised patients affected by multiple clinical conditions such as MI, HF, cirrhosis, and pulmonary infections.[15] We have also shown, for the first time, that even a moderate serum [Na+] decrease (i.e. 4.8 mmol/L) is associated with an increased risk of mortality.[15] Although these data both confirm and reinforce the strong association between hyponatraemia and poor outcomes such as inpatient mortality, it cannot prove a cause and effect relationship between these variables. Further studies are necessary to establish whether hyponatraemia has a direct effect on adverse outcomes, or is simply a marker for severity of underlying diseases.

Hyponatraemia also represents an economic and social burden. In fact, increased length of hospital stay and also hospital readmission rates have been demonstrated in hyponatraemic patients. Furthermore, economic models have estimated direct costs associated with effective correction of hyponatraemia in hospitalised patients in the US at $1.6-3.6 billion/year.[16] Therefore, hyponatraemia directly causes an increase in total healthcare costs.

Taken together, these data suggest the importance of using the most appropriate therapeutic strategies to correct this electrolyte disorder. The essential requirement to properly manage hyponatraemia is a correct diagnosis because the therapy depends strictly on the subtype and aetiology of hyponatraemia.[17] Hyponatraemia can be classified in hypotonic or non-hypotonic forms, based on plasma osmolality, which can be increased, normal, or reduced. Hypotonic hyponatraemia is the most frequent condition and can be further divided according to the extracellular volume status into hypovolaemic, euvolaemic, and hypervolaemic forms (Table 1). Another important aspect to be considered is the potential of risks associated with inappropriate treatment of hyponatraemia. In particular, an overly rapid correction of hyponatraemia may result in osmotic demyelination syndrome (ODS), a severe and potentially lethal complication.[18] The risk of ODS is particularly high when hyponatraemia is chronic because when the correction rate is too rapid, the cells may not be able to recapture the osmolytes lost through the chronic adaption mechanisms that counteract

cellular swelling and brain oedema. The result is an excessive movement of water out of the cells with consequent cellular shrinkage and osmotic demyelination. Several conditions can increase the risk of developing ODS such as hypokalaemia, hypophosphataemia, alcoholism, malnutrition, advanced liver diseases, or a serum level of [Na+] ≤105 mmol/L.[16-18]

CONVENTIONAL TREATMENT OF HYPONATRAEMIA

The treatment of hypotonic hyponatraemia, which is the most common form, depends on the presence of signs and symptoms related to the severity and rapidity of onset of the disorder (i.e. acute versus chronic) as well as on the status of the extracellular volume.[17]

The first-choice treatment of hypovolaemic hyponatraemia is isotonic (0.9% sodium chloride [NaCl]) saline infusion. Symptomatic euvolaemic and hypervolaemic hyponatraemia are effectively treated with hypertonic (3% NaCl) saline infusion and loop diuretics.[19,20] An important point to consider is the correction rate of hyponatraemia, which should not exceed a serum [Na+] correction of 8-12 mmol/L/day or 18-24 mmol/L in the first 48 hours, in order to avoid the occurrence of ODS.[16,18] Recently published expert panel recommendations[16] have suggested that a 6 mmol/L increase in serum [Na+] appears to be sufficient to reverse the most severe signs and symptoms of acute hyponatraemia. This more prudent approach can

Table 1: Classification of hyponatraemia.

Non-Hypotonic Hyponatraemia			
	Hypertonic hyponatraemia	**Isotonic hyponatraemia**	**Pseudohyponatraemia**
Causes	Hyperglycaemia, retention of mannitol, radiographic contrast.	Retention in the extracellular space of osmotically active solutes other than sodium.	Severe hypertriglyceridaemia or hyperparaproteinaemia.
Hypotonic Hyponatraemia			
	Hypervolaemic hyponatraemia	**Euvolaemic hyponatraemia**	**Hypovolaemic hyponatraemia**
Causes	Heart failure, nephrotic syndrome, acute or chronic renal failure, cirrhosis.	SIADH, hypocortisolism, hypothyroidism.	*Renal solute loss*: Diuretic therapy, cerebral salt wasting syndrome, salt wasting nephropathy, Addison's disease. *Extrarenal solute loss*: Vomiting, diarrhoea, pancreatitis.

SIADH: syndrome of inappropriate secretion of antidiuretic hormone.

be considered, especially when risk factors for the development of ODS are present.

The traditional therapeutic approach in asymptomatic euvolaemic or hypervolaemic hyponatraemia is represented by fluid restriction. This treatment has some limits in that it is usually poorly tolerated by patients because of an increased perception of thirst and the improvement of serum [Na+] is often insufficient, especially if the kidneys are not able to excrete free water.[19-21] Other possible options for the treatment of these forms of hyponatraemia include lithium, demeclocycline, and urea. However, these molecules do not have a specific indication for the treatment of hyponatraemia, their efficacy can vary, and there may be potentially severe adverse effects.[16,19] Hence, there is a need to develop new specific drugs to improve the treatment of this electrolyte disorder.

Vasopressin Receptor Antagonists: A New Therapeutic Option

In the early 1990s, the first non-peptide vasopressin receptor antagonists were identified and successfully used for the correction of hyponatraemia.[22,23] The vasopressin receptor antagonists, or vaptans, act by blocking the binding of vasopressin to Type 2 (V2) receptors on the principal cells of the renal-collecting ducts, thus causing the inhibition of the synthesis and transport of aquaporin-2 into the apical membrane, which prevents water reabsorption (Figure 1). The main characteristic of vaptans is that they produce solute-sparing water excretion, as opposed to traditional diuretics that produce simultaneous electrolyte loss.[23] This particular effect of vaptans, known as aquaresis, causes a decrease in urine osmolality and an increase in serum [Na+], thus opening up the potential use of these drugs in hypervolaemic and euvolaemic hyponatraemia. Due to this mechanism of action, it is evident that vaptans are not indicated for the treatment of hypovolaemic hyponatraemia. Four non-peptide vasopressin receptor antagonists have been tested in clinical trials: tolvaptan, conivaptan, lixivaptan, and satavaptan.[16,24] The main properties of these compounds are shown in Table 2. However, only tolvaptan and conivaptan are currently available for clinical use and therefore the remaining part of this review will be focused on these agents.
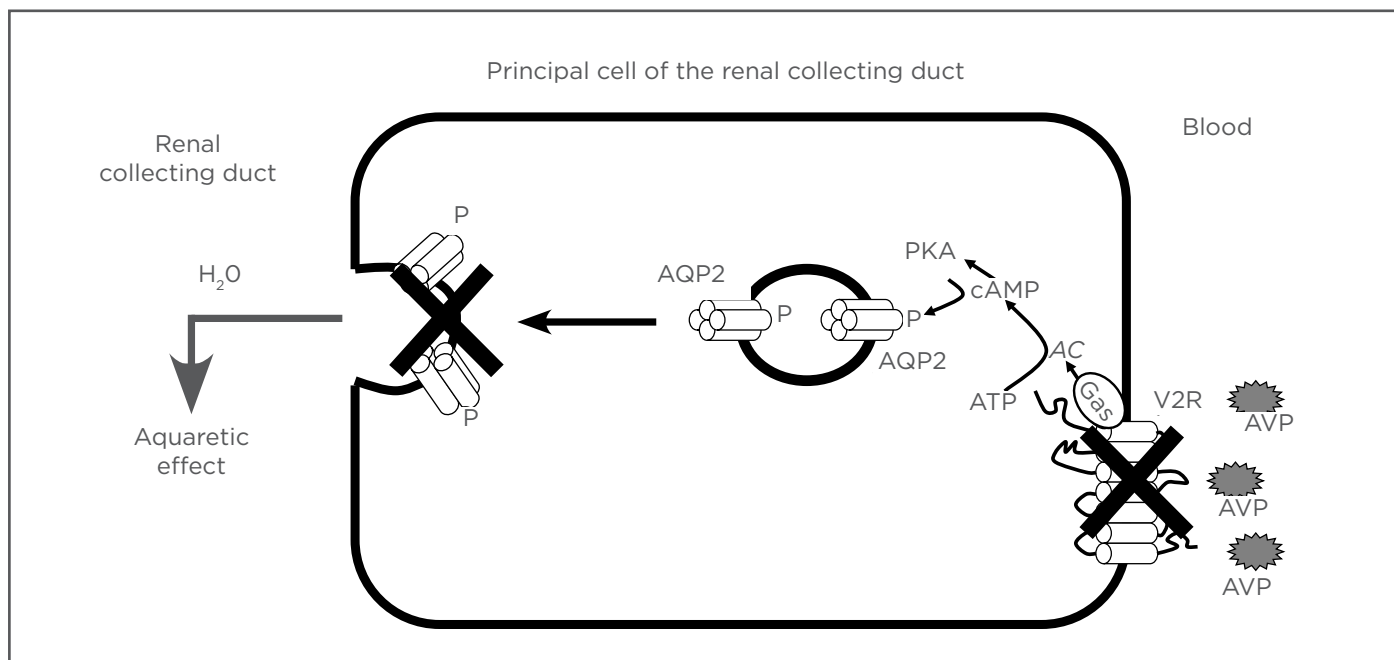

Figure 1: Vaptans mechanism of actions: binding of vaptans to V2R inhibits the activation of the Gs-coupled adenylyl cyclase cascade, thus inhibitng the synthesis, phosphorylation, and insertion of the AQP2 channels into the cell membrane. The final result is a reduction in water permeability of the renal collecting duct.
AVP: arginine vasopressin; V2R: Type 2 vasopressin receptor; AC: adenylate cyclase; ATP: adenosine triphosphate; cAMP: cyclic adenosine monophosphate; PKA: protein kinase A; AQP2: aquaporin-2; P: phosphate.

Table 2: Main properties of the vasopressin receptor antagonists evaluated in clinical trials.

	Tolvaptan	Conivaptan	Lixivaptan	Satavaptan
Receptor specificity	V2	V1a /V2	V2	V2
Route of administration	Oral	IV	Oral	Oral
Half-life (hours)	6-8	3-8	7-10	14-17
Metabolism	Hepatic	Hepatic	Hepatic	Hepatic
Dosage (mg/day)	15-60	20-40	10-400	5-50

V1a: vasopressin Type 1a; V2: vasopressin Type 2; IV: intravenous.

CONIVAPTAN AND TOLVAPTAN IN CLINICAL PRACTICE

Indications

Conivaptan, the only combined vasopressin V1a/V2 receptor antagonist available, was approved by the FDA in 2005, and can be used in the US for the treatment of euvolaemic and hypervolaemic hyponatraemia in hospitalised patients. Tolvaptan was approved by the FDA and the European Medicines Agency (EMA) in 2009 and is sold in the US for the treatment of hypervolaemic and euvolaemic hyponatraemia, whereas in Europe, its use is limited to hyponatraemia secondary to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). As already highlighted, vaptans are not indicated in hypovolaemic hyponatraemia; therefore, an accurate clinical and biochemical evaluation should always precede the use of these drugs.

Vaptans can be used to correct mildly symptomatic or asymptomatic hyponatraemia as an alternative to fluid restriction (if the latter is not tolerated or does not work effectively), or to treat moderately symptomatic hyponatraemia as an alternative to hypertonic saline solution.[25] The use of vaptans in apparently asymptomatic hyponatraemia appears to be appropriate because of the potential adverse effects on bone, nervous system, and on mortality also observed in this condition.[4-8,15] Severely symptomatic hyponatraemia presenting - for instance - with seizures, respiratory distress, or coma should still be treated with hypertonic saline solution infusion.[16] In some specific clinical settings, the use of vaptans appears particularly useful; i.e. in patients with paraneoplastic SIADH who have to start chemotherapy with drugs that could cause or worsen hyponatraemia,[26] or in patients in surgical or intensive care units, who require a readily effective treatment strategy. In Figure 2 the suggested indications for the use of tolvaptan in Europe are summarised.

It is important to highlight that vaptans should not be used together with or immediately after hypertonic saline because of the risk of overcorrection, and for that same reason, patients should be encouraged to maintain a normal fluid intake and drink in response to thirst.[16]

Pharmacological Properties

Conivaptan is the only vaptan available for intravenous use (an oral formulation has been evaluated in clinical studies but is not available for clinical use) and is restricted to the short-term treatment (of up to 4 days) for hospitalised patients. The loading dose is 20 mg over 30 minutes, followed by a continuous infusion of 20 mg/day. The dosage may be increased to 40 mg/day if the correction of hyponatraemia appears to be inadequate.[27]

Tolvaptan is available in tablet formulation. Although the treatment must be started in the hospital, it can be continued after being discharged once the optimal dose has been established. Tolvaptan use is also indicated for long-term treatment when needed to maintain serum [Na+] within the normal range. The starting dose of tolvaptan is 15 mg once daily; the dosage can be increased to 30-60 mg at intervals ≥24 hours if the correction of the serum [Na+] is insufficient.[28]
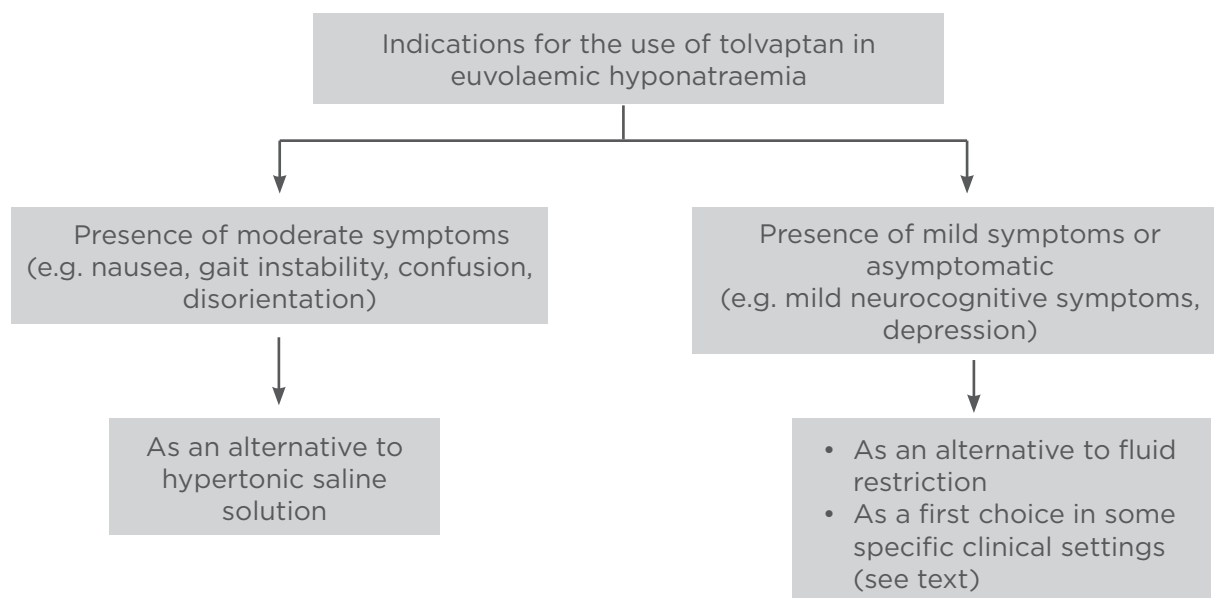
Figure 2: Indications for the use of tolvaptan in the treatment of euvolaemic hyponatraemia, according to the European indication, which restricts its use in patients with hyponatraemia secondary to syndrome of inappropriate secretion of antidiuretic hormone (SIADH).

During the active phase of correction of hyponatraemia with conivaptan or tolvaptan, it is essential to strictly monitor the serum [Na+], which should be measured every 6 hours or more frequently in patients with ODS risk factors.[17,29] In the case of tolvaptan, which can be used for a prolonged time, as already mentioned, a close measurement of the serum [Na+] is no longer necessary once the optimal dosage has been established.

The metabolism of all vaptans is hepatic, through the cytochrome CYP_3A_4 isoenzyme, and therefore, the potential interaction with CYP_3A_4 inhibitors (i.e. macrolide antibiotics, diltiazem, ketoconazole, but also grapefruit) that could increase the effect of vaptans or CYP_3A_4 inducers (i.e. rifampicin, barbiturates), which could reduce their effect, should be considered.[30,31] In contrast, tolvaptan treatment does not interfere with the serum concentrations of other CYP_3A_4 substrates, such as warfarin or amiodarone.[32,33] High and continued doses of tolvaptan (i.e. 60 mg/daily) could increase serum digoxin concentrations (mean maximal concentration: 1.27-fold increase); therefore patients treated with both tolvaptan and digoxin should be monitored for excessive digoxin effects.[33]

Efficacy

The efficacy and safety of conivaptan and tolvaptan have been demonstrated in several clinical trials involving patients affected mostly by hyponatraemia secondary to HF, cirrhosis, and SIADH. In two placebo-controlled, randomised, double-blind studies, oral conivaptan appeared to be safe and effective in increasing and maintaining serum [Na+] in patients with euvolaemic and hypervolaemic hyponatraemia. Similar results were obtained with intravenous use.[27,34] SALT-1 and SALT-2 (Study of Ascending Levels of Tolvaptan in Hyponatraemia 1 and 2) were two multicentre, randomised, double-blind, placebo-controlled trials, which evaluated the efficacy of oral tolvaptan in patients with hyponatraemia secondary to HF, liver failure, and SIADH.[28] These studies showed a higher, progressive increase in serum [Na+] in patients who received tolvaptan versus placebo, without significant side-effects. Similar results were obtained in a subsequent analysis of the SIADH subgroup.[35] Furthermore, a combined analysis of the two trials highlighted a significant improvement in the mean score of the SF-12 Mental Component Summary Scale from the baseline to day 30 in the tolvaptan group, suggesting that the increase in serum [Na+] secondary to tolvaptan therapy was clinically beneficial.

The subsequent extension of the SALT-1 and SALT-2 trials, the Safety and sodium Assessment of Long-term Tolvaptan With hyponatraemia: A year-long, open-label Trial to gain Experience under Real-world conditions (SALTWATER) trial, showed similar

results in terms of efficacy and safety.[36] Another interesting study[37] demonstrated that tolvaptan was better than fluid restriction in improving serum [Na+] (+6 nmol/L versus ≤1 nmol/L in patients treated with fluid restriction) in a cohort of hyponatraemic hospitalised patients.

Two trials conducted specifically on patients affected by HF, the ACTIV in CHF (Acute and Chronic Therapeutic Impact of a Vasopressin antagonist in Chronic Heart Failure) and the EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan), evaluated the impact of tolvaptan on survival as a secondary end-point.[38,39] In a post-hoc analysis of the ACTIV trial, a link between an improvement in hyponatraemia and in survival was observed. In the EVEREST trial, tolvaptan did not show any effects on mortality during the long-term follow-up, but in patients with moderate-to-severe hyponatraemia (<130 mEq/L) tolvaptan was associated with reduced cardiovascular morbidity and mortality after discharge.[40,41] However, it has to be specified that the EVEREST trial was not targeted to study the effects of tolvaptan on hyponatraemia, and it was not specified if the therapy was effectively associated with the normalisation of serum [Na+]. Together with the beneficial effect of not causing electrolyte depletion, these qualities make vaptans particularly useful in the treatment of hyponatraemia secondary to HF, alone or in association with traditional diuretics.[16]

The use of vaptans in patients affected by cirrhosis and renal failure appears more controversial. Furthermore, after a recent alert regarding liver toxicity due to high doses of tolvaptan (see adverse events section), the FDA has contraindicated the use of tolvaptan in patients with underlying liver diseases. In patients with hyponatraemia secondary to nephrotic syndrome and concomitant renal failure, vaptans are not expected to cause a significant aquaretic effect, in particular if the glomerular filtration rate is <50 ml/min or the serum creatinine is >3 mg/dl and its use is not recommended.[16]

Safety and Adverse Events

Conivaptan and tolvaptan are generally well tolerated. The most frequent side-effects are headache, orthostatic hypotension, nausea, increased urinary frequency, and hypokalaemia. Thirst and dry mouth are two common and expected consequences of the aquaretic effect of these drugs.[27,42]

The safety of tolvaptan was confirmed in the SALT-1, SALT-2, and SALTWATER trials, in which an overly rapid correction of serum [Na+] or hypernatraemia were rarely observed (<2% of treated cases).[28,35,36] Nevertheless, both the FDA and EMA have remarked on the necessity of monitoring the fluid and electrolytic balances in patients treated with tolvaptan or conivaptan, following the occurrence of a few ODS cases in patients treated with tolvaptan. However, only one case of ODS occurring after correction of hyponatraemia with tolvaptan alone has been reported very recently.[43] Even though a causal relationship to drug exposure has not been clearly established, a strict monitoring of serum [Na+] in the active phase of correction of hyponatraemia is recommended, especially in patients with serum [Na+] ≤120 mmol/L, in which greater responses have been documented.

Active therapy should be stopped if the rate of correction exceeds 8-12 mmol/L in the first 24 hours (or 18 mmol/L within 48 hours), in agreement with the general recommendations for the correction rate of hyponatraemia. The possible overly rapid increase in serum [Na+] can be limited by stopping the drugs (which both have a half-life <12 hours). Serum [Na+] re-lowering may be optional in patients at low-to-moderate risk of ODS, but is recommended in patients at high risk. This objective can be achieved by infusing or orally administering hypotonic fluids. The use of desmopressin can also be considered to obtain serum [Na+] re-lowering.[16,25]

Recently, the FDA issued an additional warning relating to the potential hepatotoxicity associated with tolvaptan treatment, following the report of a few cases of liver toxicity in patients enrolled in a 3-year trial examining the effects of tolvaptan for a different indication, i.e. for the treatment of autosomal dominant polycystic kidney disease (ADPKD) (TEMPO trial, for Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and its Outcomes).[44] A reversible increase in serum alanine aminotransferase and total bilirubin was observed in three patients treated with tolvaptan, and this effect was related to the administration of this drug. In October 2013 the FDA determined that tolvaptan should not be used for longer than 30 days nor in patients with underlying liver diseases because it can cause an increased risk of liver injury. However, it has to be said that the dosage used in the TEMPO trial was much higher than

the maximum dose approved for hyponatraemia treatment (120 mg versus 60 mg/daily).

Moreover, in clinical trials where the FDA-approved doses of tolvaptan were used (e.g. the SALTWATER and EVEREST trials), hepatic injury was not reported. In agreement with these aspects, the EMA has not limited the long-term use of tolvaptan but suggested to perform liver function tests in patients treated with tolvaptan who have reported symptoms suggesting liver injury (i.e. fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice). Therefore, in patients who could benefit from the long-term use of tolvaptan, the therapy can be confirmed provided that a careful follow-up is maintained. However, the drug must be stopped if liver damage is suspected. Tolvaptan can be re-initiated when it has been clearly established that liver toxicity is not related to treatment with this drug. The use of tolvaptan in patients affected by liver diseases should be evaluated with caution and preferably avoided.[16] In some particular cases - i.e. in the patients already listed for liver transplantation with severe hyponatraemia, which could increase the surgical or anaesthesiological risk - the therapy could be considered because the potential benefit from the correction of hyponatraemia may outweigh the risk.[16]

FINAL CONSIDERATIONS

Vaptans appear to be an effective and substantially safe therapeutic option for the treatment of hypotonic hypervolaemic (US) and euvolaemic (US and Europe) hyponatraemia. In particular, in patients with mild-to-moderate symptomatic hyponatraemia, or in those with asymptomatic hyponatraemia, the use of these drugs appears to be an appropriate treatment strategy as an alternative to traditional treatments. The use of conivaptan is limited to short-term therapy of hospitalised patients; in the US, conivaptan is the only vaptan available in patients who cannot receive oral therapy because it can be administered intravenously. Furthermore, conivaptan appears to be particularly useful in patients affected by HF because it has a dual selectivity, i.e. for V1a and V2 receptors. Tolvaptan can also be used for long-term treatment provided that a careful evaluation of possible signs suggesting adverse events is carried out. Admittedly, the cost of this drug may very well be a current limit for its prolonged use. Further studies are required in order to clarify the effective advantages of this class of drugs in terms of cost-effectiveness and patient outcomes.

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