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Current and future treatment options in SIADH

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Abstract

The treatment of hyponatraemia due to SIADH is not always as straightforward as it seems. Although acute treatment with hypertonic saline and chronic treatment with fluid restriction are well established, both approaches have severe limitations. These limitations are not readily overcome by addition of furosemide, demeclocycline, lithium or urea to the therapy. In theory, vasopressin-receptor antagonists would provide a more effective method to treat hyponatraemia, by virtue of their ability to selectively increase solute-free water excretion by the kidneys (aquaresis). In this review we explore the limitations of the current treatment of SIADH and describe emerging therapies for the treatment of SIADH-induced hyponatraemia.

Keywords: hyponatraemia; SIADH; urea; vasopressin; vasopressin-receptor antagonist

Introduction

Hyponatraemia is associated with increased morbidity and mortality, but it is frequently under-recognized and undertreated [1]. In the absence of end-stage renal failure, hyponatraemia usually represents a state of vasopressin-induced water retention. The cause of the increased plasma vasopressin concentration can be volume depletion, in which case the water retention can be viewed as appropriate from a circulatory point of view. Another type of hyponatraemia occurs in so-called hypervolaemic states (cardiac failure, liver cirrhosis). However, in still other instances vasopressin-induced water retention occurs as a result of a hyper- or hypovolaemia-independent increase in vasopressin secretion. There may also be an increase in the renal actions of vasopressin on its receptor [2]. In patients with the latter two entities, antidiuresis is deemed 'inappropriate', hence the name Syndrome of Inappropriate Anti Diuretic Hormone secretion (SIADH). For instance, uncontrolled vasopressin secretion may occur in patients with small-cell cancer of the lung. In these patients urine is not maximally dilute, despite the reduction in serum osmolality. In some patients SIADH is episodic in occurrence, but in others it is chronic, lasting for years. In such subjects, long-term treatment may be necessary. Although there are several approaches to the treatment of SIADH, none of the present treatment options is without problems [3].

Before delving into specific forms of treatment, one should consider the question: 'Are all patients with SIADH alike?' Although vasopressin levels appear largely independent of serum osmolality in roughly one third of the patients, many patients exhibit some form of vasopressin responsiveness albeit at a lower serum osmolality [2]. In such cases, excessive fluid intake appears equally important to vasopressin release in the initiation of hyponatraemia. This may be due to regulation at a lower setpoint (i.e. a 'reset osmostat') [2]. Because serum osmolality is still regulated in these patients, a correction of the hyponatraemia causes excessive thirst, which leads to persistent hyponatraemia that can be erroneously interpreted as 'treatment failure'. In rare patients a renal form of inappropriate antidiuresis has been described, due to an activating mutation in the vasopressin receptor [4]. In these patients plasma vasopressin levels are low or even undetectable at all levels of serum osmolality. Not all patients with drug-induced SIADH have measurable plasma levels of vasopressin, suggesting that modulation of the vasopressin-receptor aquaporin-2 signalling pathway may also occur [5]. Indeed, in SIADH the range of plasma copeptin levels (a stable 39-amino acid peptide derived from the same precursor protein as vasopressin) was significantly lower than in patients with hypovolaemic hyponatraemia [6]. Plasma copeptin levels give an estimate of long-term vasopressin secretion, much like HbA1C percentages in diabetes; this implies that vasopressin-independent mechanisms may be operative [7]. Moreover, it must be remembered that thirst and drinking play an important role in the pathogenesis of hyponatraemia. This was illustrated in rats in which exogenous DDAVP was followed by suppression of thirst and only the combination with forced water intake led to hyponatraemia [8].

Current treatment options

Water restriction

As the hypo-osmolality in SIADH results from a relative abundance of water in the intra- and extracellular volumes,

maintained by a reduced ability to excrete water, restriction of oral water intake is a logical option [9]. In general a fluid restriction of 0.8 L/day is advised. This includes all fluids, including water contained in food. As the obligatory diuresis due to osmole excretion, together with insensitive water loss through the skin, gut and lungs, generally exceeds this amount, a small amount of free water is lost in the urine. This strategy leads to a slow correction rate. In these patients, the advised rate of correction should be viewed as a maximum rather than a target [10]. At the present time, water restriction is generally considered the treatment of choice for hyponatraemia secondary to SIADH. However, many patients have difficulties complying with prolonged fluid restriction, possibly because they experience "inappropriate" thirst, and hyponatraemia may recur [11]. Moreover, in patients with SIADH part of the water overload may be due to downward resetting of the osmotic threshold for thirst [12]. As thirst is particularly difficult to suppress [13], water restriction in SIADH frequently leads to noncompliance in the long run. The use of water restriction is insufficient to treat acute severe hyponatraemia and should not be employed in severely symptomatic hyponatraemia, in which a more rapid correction rate is necessary.

Isotonic saline

As urine osmolality in SIADH frequently ranges from 400–600 mOsmol/kg, infusion with isotonic saline may lead to a further decrease in serum osmolality. A frequent misconception is that isotonic saline (300 mOsmol/kg) is hypertonic to the patient and should therefore lead to correction of hyponatraemia. However, when the infusate (Na) is lower than the patient's urinary (Na + K), the use of isotonic saline represents a source of free water. This process is referred to as desalination [14]. This is most likely to occur if urinary osmolality is above 530 mOsm/kg, as some patients with SIADH and lower urinary osmolalities have been successfully treated with isotonic saline [15].

Hypertonic saline

If a patient is symptomatic due to a rapid decrease in serum sodium concentration, treatment with hypertonic saline should be considered [16]. No randomized trials have ever been performed comparing different approaches to acute correction of hyponatraemia, but the use of hypertonic saline in this circumstance is widely accepted [11,17]. Hypertonic saline may or may not be combined with a loop diuretic, depending on the volume status of the patient [18].

Several formulae have been developed to estimate the effect of a given infusate on the serum sodium concentration. A simple rule of thumb that was recently proposed: In order to induce a correction rate of 1 mmol/L per hour, using 3% NaCl, one should infuse the body weight as millilitres per hour (i.e. a man with a body weight of 70 kg will increase by approximately 1 mmol/L per hour when infused with 3% NaCl at a rate of 70 mL/h) [19].

The Adrogué–Madias formula has been most extensively studied [11,20,21]. This formula was shown to predict correction rates using hypertonic saline with reasonable accuracy, and is listed below. The formula derives the change in plasma sodium concentration (Δ[Na]) that is produced by 1 l of infusate with given sodium and potassium concentrations ($[Na]_{infusate} + [K]_{infusate}$) from the present serum sodium concentration and the (new) volume of distribution (total body water + 1).

$$\Delta[Na] = ([Na]_{infusate} + [K]_{infusate}) - \text{serum [Na]}/\text{total body water} + 1.$$

It should be noted that this formula does not consider ongoing urinary loss of sodium and potassium. In addition, it sometimes underestimates the rate of correction of hyponatraemia following hypertonic saline, leading to potential over correction [21]. Therefore, irrespective of the way the initial rate of infusion was derived, a close follow-up of the patient and frequent determinations of the serum sodium concentration and/or urine osmolality are essential.

Loop diuretics

In order to increase free water excretion rates, loop diuretics have proven effective in the treatment of SIADH. This may be related to an inhibition of the ability of the kidney to maintain a medullary concentration gradient [22]. This treatment, however, is not useful in long-term treatment of SIADH, as a few results of long-term treatment have been reported and this strategy is generally reserved to the acute phase of correction [23]. In patients in which fear exists for the development of pulmonary oedema during treatment with hypertonic saline, treatment with loop diuretics can help in avoiding vascular overfilling.

Demeclocycline

Nephrogenic diabetes insipidus (NDI) is a frequent renal side effect of demeclocycline hydrochloride, a group I tetracycline derivative. For this reason, it is occasionally used to treat SIADH. Its use dates back to the 1970s [24] and the drug has been employed chronically, most often in patients with SIADH due to a malignancy [25]. However, the agent has frequent side effects, such as nausea and skin photosensitivity. Moreover, demeclocycline has also been shown to cause nephrotoxicity [26], in some cases leading to irreversible renal failure [27]. At present, it is unknown where it interferes with the vasopressin-aquaporin signalling cascade [28]. It causes NDI in roughly 70% of cases and it takes 2–3 days before it becomes effective.

Lithium

Like demeclocycline, lithium carbonate causes NDI in some 65% of patients. Patients with bipolar disorder generally respond well to lithium treatment, but the side effects on urinary concentrating ability often cause polyuria and polydipsia. Lithium appears to enter the principal cells of the collecting duct through the epithelial sodium channel ENaC and reduces aquaporin-2 expression [29]. Long-term treatment with lithium may induce tubulo-interstitial nephritis that can lead to irreversible NDI and end-stage renal failure [30]. The effect of lithium takes approximately 4 days to set in. The serum lithium concentration must be followed

closely in order to prevent renal toxicity. For these reasons, the use of lithium to treat SIADH has been mostly abandoned. In animal models, however, lithium has been shown to augment the effects of aquaretic agents [31].

Urea

Urea is a major osmotic constituent of urine, accounting for half of the daily osmolar load excreted. In classic experiments, Brodsy and Rapoport demonstrated that as solute excretion increases, the osmolality of urine decreases, despite maximal doses of vasopressin [32]. This has led investigators to pursue the effects of increasing free water clearance by administering urea [33]. Urea can be given by mouth, either as a powder or in capsules, and thus results in an osmotic diuresis. Due to its bitter taste, its use has not met wide acceptance, but Decaux *et al*. have reported favourable results of long-term treatment [34]. Interestingly, in animal models the use of urea appears to protect against brain damage and myelinolysis during rapid correction of hyponatraemia [35,36]. Both a high-protein diet and urea administration ameliorated hyponatraemia in rodents and was associated with a decrease in natriuresis [37]. Its use appears to be restricted to patients with moderately elevated urinary osmolalities [38].

Extracorporeal treatments

Although rapid correction of hyponatraemia may occur during haemodialysis, in some instances leading to pontine myelinolysis [39], more gradual forms of dialysis treatment have been advocated. Veno-venous haemofiltration has been shown to induce a more gradual correction of hyponatraemia [40] and other forms of slow dialysis treatment, such as slow low-efficiency daily dialysis (SLEDD), may be equally effective [41]. However, as most forms of continual renal replacement therapy are performed on intensive care wards, this approach to treat SIADH would lead to a steep increase in costs. In patients with established renal failure, however, dialytic or convective therapies are the treatment of choice.

Vaptans

As current forms of treatment of SIADH have serious limitations, the development of the new class of orally available aquaretic agents was received with great expectation [42]. In the absence of treatment directed at aquaporin-2 expression, the next most specific treatment of SIADH would be to inhibit the effects of vasopressin, using a vasopressin-receptor antagonist, also called 'vaptans' (Figure 1) [17]. In the past 15 years, several studies have explored the use of these aquaretic drugs in hyponatraemia (Table 1). In these studies, an effort was made to distinguish between patients with euvolaemic, hypervolaemic and hypovolaemic forms of hyponatraemia, because giving a vaptan in the presence of hypovolaemia would have detrimental effects. One of the diseases that appeared to be a prime indication for the new vaptan-class of drugs was SIADH. The effectiveness of tolvaptan, a selective vasopressin V2-receptor antagonist, in increasing serum sodium concentrations was demonstrated in the SALT-1 and SALT-2 trials (Figure 2) [43]. Although these 30-day trials of tolvaptan also included patients with hyponatraemia due to heart failure and liver cirrhosis ('hypervolaemic hyponatraemia'), some 40% of the participants were diagnosed with SIADH. As euvolaemia is often difficult to assess in such patients [44], saline infusions were used when there was doubt concerning the volume status. Participating patients were no longer required to adhere to a fluid restriction. In general, treatment appeared to be effective and to have an acceptable safety profile. The most common side effects were increased thirst and a dry mouth. The desirable rates of correction of serum sodium were exceeded in only 4 out of 223 patients, and an overshoot of the sodium concentration to levels above 146 mmol/L was observed in no more than 4 patients [43]. However, the protocol mandated strict monitoring of the serum sodium concentration. It remains to be seen how safe the agent will turn out to be in everyday clinical life.

As these studies included patients with varying underlying disease, and no data were given for individual patient groups, it remains difficult to use the outcome of this study as guidance for therapeutic intervention in SIADH. Although scores on the Physical Component Summary of the SF-12 health survey did not differ significantly between treated and untreated subjects, patients included in SALT-1 reported a significant increase in the Mental Component Summary [43].

A study on the effects of conivaptan, a vasopressin V1a/V2-receptor antagonist, in hyponatraemia demonstrated its efficacy in increasing serum sodium, but included predominantly heart failure patients [45]. Although conivaptan may have effects similar to tolvaptan, conivaptan is only available as a parenteral preparation.

Following these efficacy trials, a major study was undertaken attempting to demonstrate differences in outcome of heart failure patients treated with tolvaptan, the EVEREST trial [46]. This trial failed to show significant differences in mortality compared with placebo.

A few studies have been performed to study the efficacy of vaptans specifically in SIADH patients. Several studies of short duration reported that vaptans were efficacious in increasing serum sodium concentrations [47,48]. There is, however, a paucity of long-term observations in SIADH. In one open-label extension of a satavaptan trial, SIADH-patients remained normonatraemic up to 12 months of treatment [49]. In this study, treatment was well tolerated and no patients were excluded due to side effects, although an increase in thirst was reported. Recently, two controlled trials of conivaptan were reported, both performed in a limited number of patients with euvolaemic or hypervolaemic hyponatraemia, mostly due to SIADH [50,51]. Both studies demonstrated efficacy of conivaptan to increase free water clearance and to correct hyponatraemia. In a subsequent report on a subgroup of patients that were considered euvolaemic (including a higher percentage of patients with SIADH), similar results were obtained [52].

Although long-term studies performed specifically in SIADH patients are awaited, there is little doubt that these agents will be effective in the treatment of chronic hyponatraemia [53,54]. However, at present, all treatment-related recommendations are based on expert opinion and there

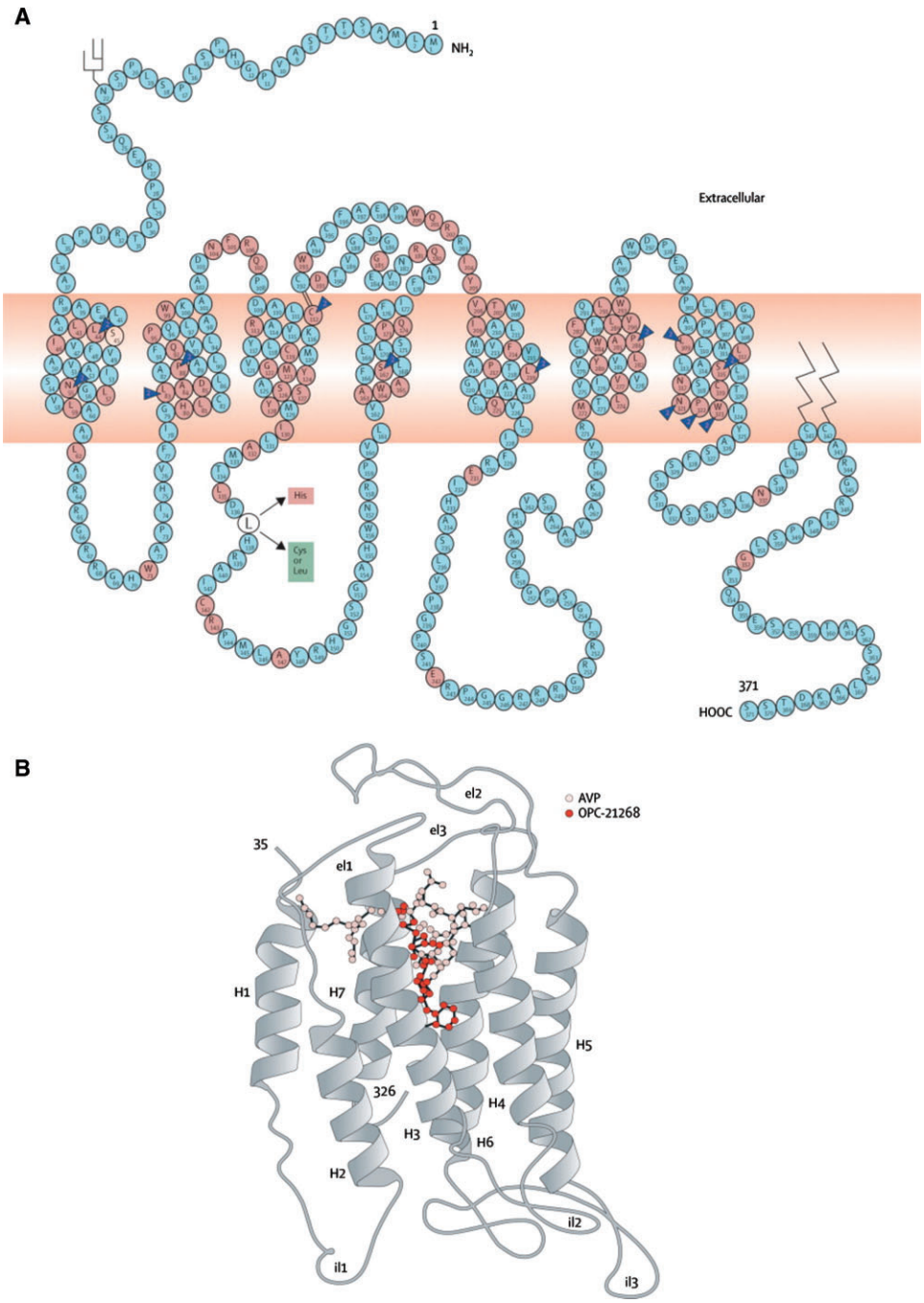

Fig. 1. The vasopressin V2-receptor, vasopressin, and a non-peptide vasopressin receptor inhibitor (OPC-21268). (**A**) Vasopressin-2 receptor with its seven transmembrane helices. Red dots indicate the loss-of function mutations in patients with nephrogenic diabetes insipidus, while the two green squares indicate to gain-of-function mutations in patients with nephrogenic syndrome of inappropriate antidiuresis. (**B**) Molecular modelling of antagonist activity of vaptans. The proposed mechanism is that the vaptans penetrate deeper and more selectively into the binding pocket of the vasopressin-receptor type 2 than native vasopressin without activating it, thereby exerting an antagonistic effect. Reprinted from The Lancet, 371, Decaux, G., A. Soupart, and G. Vassart, Non-peptide arginine-vasopressin antagonists: the vaptans. 1624–1632. Copyright 2008, with permission from Elsevier.

are several issues that need to be addressed before final recommendations can be made.

In which patients could vaptans be used? In treating patients with moderate to severe symptomatic hyponatraemia, the treating physician faces a classic dilemma. The physician needs to avoid treating acute hyponatraemia too slowly (in order to prevent damage from cerebral oedema) but he also needs to avoid treating chronic hyponatraemia too quickly (in order to reduce the risk of osmotic

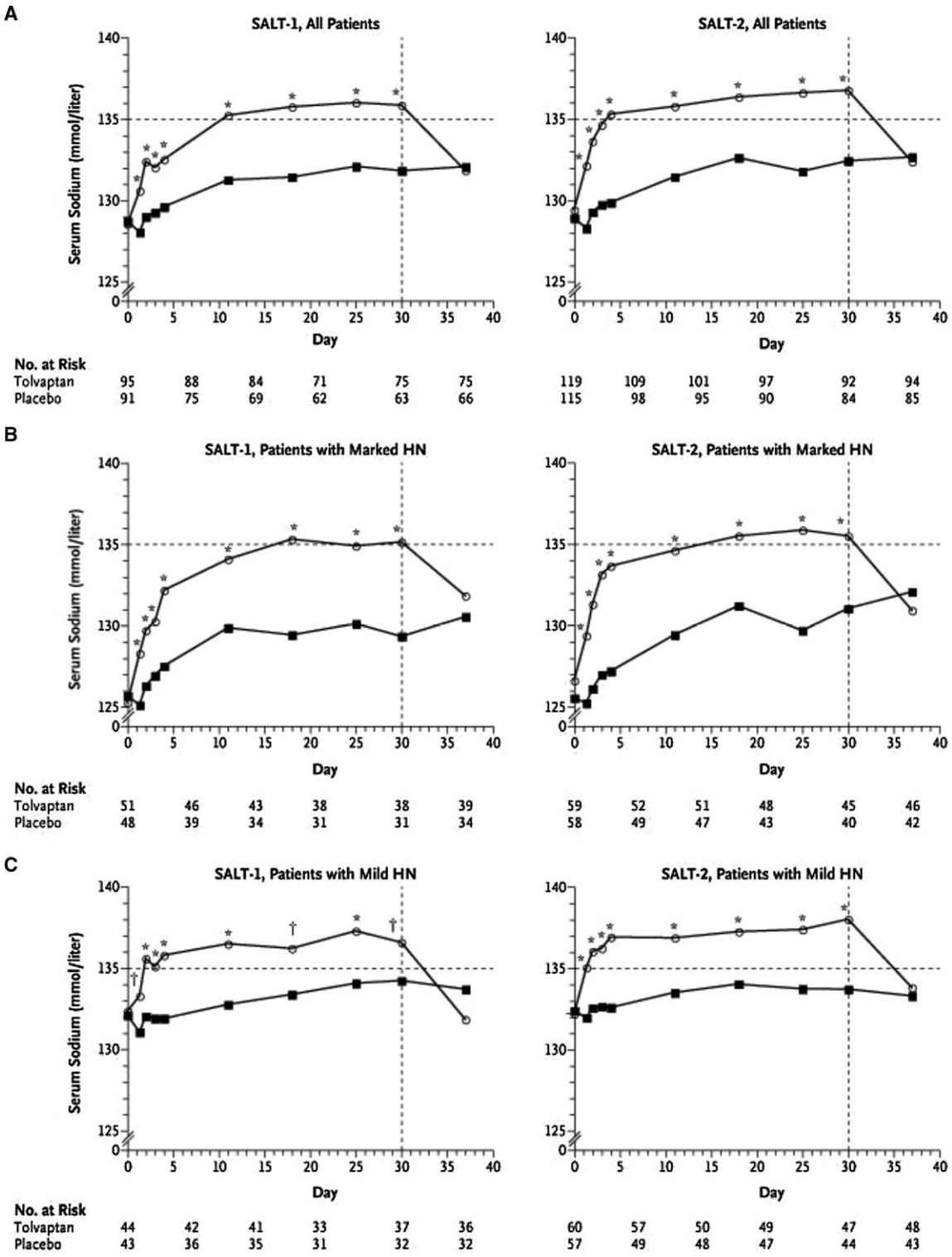

Fig. 2. Effect of Tolvaptan on serum sodium concentration in SALT-1 and SALT-2 trials. Comparison of mean serum sodium concentrations according to the day of patient visit in patients with hyponatraemia (HN) due to SIADH, liver cirrhosis or congestive heart failure receiving either tolvaptan (circles) or placebo (squares). Asterisks ($P < 0.001$) and daggers ($P < 0.01$) indicate significant differences. SALT-1 and SALT-2 refer to Study of Ascending Levels of Tolvaptan in hyponatraemia 1 and 2, two identical phase 3 randomized controlled trials in the United States of America (SALT-1) and Europe (SALT-2). Panel A shows the results of all patients, panel B of those with marked hyponatraemia (baseline serum sodium between 125 and 127 mmol/L) and Panel C of those with mild hyponatraemia (baseline serum sodium approximately 132 mmol/L). Tolvaptan was given orally for 30 days followed by a 7-day observation period. Reprinted with permission from Massachusetts Medical Society (Schrier, R.W. *et al*., Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. N Engl J Med, 355(20), 2099–2112)

Table 1. Vasopressin-receptor antagonists: characteristics and results from studies

Agent	Vasopressin receptor	Route of administration	Urine volume	Urine osmolality	Disorders studied	References
Conivaptan	V_{1a} and V_2	Intravenous or oral	↑	↓	SIADH, CHF	[45,50,52,61–63]
Lixivaptan	V_2	Oral	↑	↓	SIADH, CHF, cirrhosis	[64–66]
Mozavaptan	V_2	Oral	↑	↓	SIADH, cirrhosis	[67,68]
Satavaptan	V_2	Oral	↑	↓	SIADH, cirrhosis	[49,69]
Tolvaptan	V_2	Oral	↑	↓	SIADH, CHF, cirrhosis	[43,46,70–72]

demyelination). The problem is that distinguishing acute from chronic and symptomatic from asymptomatic hyponatraemia is not always as simple as it sounds. Moreover, the evidence upon which correction rates are based is relatively small. In correction of severely symptomatic hyponatraemia, a rapid increase of serum sodium is desirable. An increase by as little as 2–4 mmol/L may relieve symptoms, and treatment should be interrupted once symptoms abate, a safe serum sodium concentration is reached (generally $\geq$120 mmol/L), or a total magnitude of correction of 18 mmol/L is achieved [19]. When treating patients with chronic hyponatraemia, adhering to correction rates less than 10–12 mmol/L in the first 24 h (and $<$ 18 mmol/L in 48 h) will generally avoid osmotic demyelination [55], although in patients with anorexia or hypokalaemia even slower correction rates are advisable [56].

Present treatment options do not always lead to a predictable and well-controlled increase in serum sodium concentrations and calculations may lead to underestimating rates of correction [21]. However, at present, the relative efficacy of vaptans compared to hypertonic saline, is not known either. In patients with severe symptoms (seizures or coma) possibly related to acute hyponatraemia, a rapid correction rate is initially desirable and the current treatment of choice is to give hypertonic saline. There is no documented experience using vaptans in patients with serum sodium concentrations below 120 mmol/L.

If vaptans were to be proven to lead to a more predictable rise in serum sodium concentrations, either as initial treatment or as sequential treatment following hypertonic saline, with greater effectiveness compared to fluid restriction, this could potentially reduce the length of hospitalization and thereby cost. Presently, no studies have been reported directly comparing the efficacy of hypertonic saline infusion to that of treatment with vaptans.

Patients with chronic SIADH and persistently elevated levels of vasopressin will also be obvious candidates for oral vaptans. However, in patients with chronic, mild to moderate, hyponatraemia (120–133 mmol/L) water restriction has generally been the initial therapy [19]. However, fluid restriction is usually a burden to the patient, unreliable, impractical and slow to work. It would seem that vaptans would be especially suited for treatment of these patients. As increased thirst is a frequent feature of hyponatraemia in SIADH, in such patients vaptans may prove to be more effective than fluid restriction. Indeed, in most studies reported to date, serum sodium concentrations were corrected by vaptans, despite lifting of the fluid restriction [43,50]. Hence, vaptans may substantially improve the quality of life in these patients.

In which patients should vaptans not be used? As previously mentioned, no data are available on the use of vaptans in the treatment of severe symptomatic hyponatraemia (serum sodium $<$120 mmol/L), and it would seem prudent not to treat these patients with a vaptan at the present time. Until further data become available, hypertonic saline should be given in these patients.

Oral vasopressin-receptor antagonists are contraindicated in patients with hypovolaemic forms of hyponatraemia, because the subsequent decrease in extracellular fluid volume would be deleterious. In theory, when using selective V2-receptor antagonists, the subsequent water diuresis in these patients would be restricted by a low distal delivery [10]. As conivaptan also possesses V1a-receptor inhibitory properties, that may cause hypotension in the presence of hypovolaemic hyponatraemia, it may be even more important to avoid treating hypovolaemic patients with this specific drug. Obviously, volume replacement with 0.9% saline (with frequent determinations of urine output and serum sodium) would be the appropriate treatment here.

The problem is that volume status is not always easy to estimate clinically [57]. In general, if the sodium concentration in the urine is above 40 mmol/L, in a patient with preserved renal function, normal dietary salt intake and not on diuretics, one can assume with reasonable safety that the patient is not volume depleted.

Although probably rare, in some patients following a subarachnoidal haemorrhage renal salt wasting with cerebral disease may occur. This problem was previously referred to as cerebral salt wasting and is characterized by natriuresis despite volume depletion [58]. As volume status is difficult to assess, these patients are difficult to distinguish from SIADH patients, but should be treated with copious infusions of 0.9% NaCl and not with a vaptan.

SIADH is a diagnosis *per exclusionem*, which means that diuretic use and adrenal insufficiency should be excluded before initiating aquaretic treatment. Interestingly, although thiazide-induced hyponatraemia is typically classified as 'hypovolaemic', these patients rarely exhibit true volume depletion [59] and hyponatraemia seems largely related to vasopressin secretion and excess water intake [60]. In most of these patients discontinuation of the diuretic will suffice.

Finally, oral vasopressin-receptor antagonists are also contraindicated in patients with anuria, volume depletion, hypernatraemia or in those who cannot perceive thirst, and, in addition, during pregnancy or breastfeeding.

How should treatment be monitored? Most studies on vaptans that have been performed lasted for days to weeks.

Although the cause of hyponatraemia is frequently of a temporary nature (pulmonary disease, drug treatment), some patients require chronic treatment (chronic SIADH). This may result in the problem of not knowing when to stop treatment with a vaptan. It has been assumed that the occurrence of hypernatraemia would indicate the end of an indication. However, there is a distinct possibility that thirst caused by a rise in serum osmolality, could lead to increased water intake that would prevent hypernatraemia. Therefore, one may have to consider discontinuation of a vaptan every 6–8 weeks, in order to observe whether hyponatraemia recurs, before treatment is continued.

Are all vaptans created equal? At present the aquaretic agents can be divided into those that selectively inhibit the V2-receptor and those that have a combined antagonistic effect on V1a- and V2-receptors (Table 1). At present no studies have directly compared the effectiveness of selective V2- and combined V1a/V2-receptor inhibition in hyponatraemia, and the practical importance of these findings remains to be determined.

Conclusion

Many more questions need to be answered before one can make well-founded recommendations for the use of vaptans in treating patients with hyponatraemia due to SIADH. Future trials should address the possible superiority of vaptans to hypertonic saline in treating acute hyponatraemia. In chronic treatment, the advantages in terms of effectiveness and quality of life, as compared to water restriction, certainly require further study. However, as some of these agents are now registered for the treatment of euvolaemic hyponatraemia, one can only hope treating physicians will apply these drugs with the same amount of care as exhibited in patients that were included in the recent trials.

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