V2-antagonists for the treatment of hyponatraemia*

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Hypotonic hyponatraemia results from an excess of total body water relative to the exchangeable sodium and potassium pool due to a decrease in electrolyte-free water (EFWC) excretion [1]. The decrease in free water excretion is mostly due to the secretion of the antidiuretic hormone (ADH), also called vasopressin. This secretion is either ‘appropriate’ when it is a result of volume stimuli, or ‘inappropriate’, as in the syndrome of inappropriate secretion of ADH (SIADH), when osmotic or volume stimuli are lacking. Vasopressin is involved in most cases of sustained hyponatraemia. Therefore, the use of specific blockers of vasopressin receptors is a logical approach in the treatment of patients with SIADH or hypervolemic hyponatraemia and may offer advantages over current available therapies (Table 1: treatment of SIADH).

Selective non-peptide V2-receptor antagonists (V2RA, collectively known as the ‘vaptans’) are currently in development and in phase III trials: OPC41061 (Tolvaptan), VPA 985 (Lixivaptan), YM 087 (Conivaptan: V1a + V2 antagonists), OPC 31260 (Mozavaptan) and SR 121463B (Satavaptan). Recently, Conivaptan (Vaprisol, Astellas) has been approved for parental use in the United States for SIADH and Mozavaptan for paraneoplastic SIADH in Japan. Some published studies with these ‘vaptans’ have been conducted in hyponatraemic patients with cirrhosis [3,4], congestive heart failure [5] and patients with SIADH [6], showing their effectiveness in increasing EFWC in various water-retention disorders.

Recently, Schrier et al. reported the results of two large multicentre, randomized, placebo-controlled, double-blind trials of oral Tolvaptan in subjects with hyponatraemia and chronic heart failure, cirrhosis, SIADH or other causes. Patients were randomly assigned to oral placebo (223 patients) or oral Tolvaptan (225), at a dose of 15 mg daily. The dose of Tolvaptan was increased to 30 mg daily and then to 60 mg daily, if sodium concentration remained <135 mmol/l and had increased <5 mmol/l during the 24 h after the initial dose. Tolvaptan was stopped after 30 days and serum sodium (SNa) was measured again one week later. Mild hyponatraemia was defined as 130–134 mmol/l (50% of the patients) and marked hyponatraemia as <130 mmol/l. All the patients seemed to be asymptomatic.

One difference with other studies with V2RA was that water restriction was not prescribed to these patients. Urine output in the placebo group was, for example, 2079 ml ± 1534 ml and fluid intake 1492 ml ± 945 ml in the first day of the study. Therefore, many hyponatraemia patients had a fluid intake > 21 a day! This probably explains why the daily increase in SNa was lower than in other studies (the first day of treatment induced an SNa increase of about 2–3 mmol/l and about 7 mmol/l at the end of the study, on day 30). Around 55% of the patients in the Tolvaptan group had a normal SNa after one month of therapy and 25% in the placebo group. When Tolvaptan was stopped, SNa decreased again. The safety profile of the drug was excellent, except for an increased thirst, dry mouth and increased urination.

A pre-specified combined analysis explored the effects of the drug on physical and mental health, using self-assessed scores on the Physical Component Summary and the Mental Component Summary (on a scale range going from 8 to 73 with higher score indicating better functioning) of the SF-12 Health Survey. Physical health did not improve, although mental health showed minimal (by two or three points), but significant improvement in the Tolvaptan group when comparing baseline to day 30.

Most patients with chronic hyponatraemia and SNa > 120 mmol/l are usually considered asymptomatic [7], and while it is known that the presence of hyponatraemia is associated to an increase in morbidity and mortality [8–10], this is usually considered to be due to the severity of the underlying diseases. However, it has recently been shown that mild hyponatraemia is...
(i) High-ceiling diuretics (combined with high salt intake with or without potassium sparing diuretic (Amiloride, Triamterene).

(ii) Urea

(iii) ADH antagonists on the collecting tubule:

- Lithium
- Demeclocycline
- Orally active non-peptide vasopressin V2-receptor antagonist (in development):
  - OPC 31260 (Mozavaptan, on the market in Japan for paraneoplastic SIADH)
  - VPA-985 (Lixivaptan)
  - OPC 41086 (Tolvaptan)
  - SR 121 463 B (Satavaptan)
- Orally active non-peptide vasopressin V2 and V1 receptor antagonist:
  - YM 087 (Conivaptan, on the market in USA as an intravenous preparation for exclusive use in SIADH).

(iv) Urea

(v) High-ceiling diuretics (combined with high salt intake with or without potassium sparing diuretic (Amiloride, Triamterene).

associated with reversible attention deficit and gait instability, which induce a high incidence of fall and hospitalizations and likely bone fractures [11].

In the study of Ascending Levels of Tolvaptan in hyponatraemia (SALT) study and in all other studies, patients with severe hyponatraemia were not included (SNa < 115 mmol/l), as patients had to be ‘asymptomatic’ on usual clinical criteria to give their informed consent. Too large a correction of SNa was only rarely observed in this study (2.5%) and treatment overshoot (SNa > 145 mEq/l) was also rarely observed (5%). Excessive correction of hyponatraemia is a hazardous situation, with major risks for brain damage (myelinolysis) and neurological sequelae [12]. Careful approach of patients with sustained hyponatraemia implies a limited correction below 12 mmol/l per 24 h (and <18 mmol/l per 48 h) and even <8–10 mmol/l per 24 h, for patients with additional risk factors for myelinolysis [13].

Like with the other therapies, excessive correction with V2RA could produce osmotic demyelination [14]. Good control and limited correction are achievable by use of titrated doses of V2RA during the initial phase of correction, especially in patients with severe hyponatraemia (<115–120 mmol/l). Indeed, most published cases of myelinolysis were reported in patients with initial SNa < 115 mmol/l [15]; these patients were not included in the different V2RA studies.

Despite the attractiveness of using a pure aquaretic agent to correct life-threatening hyponatraemia, insufficient data are available from clinical trials to know if sufficiently rapid correction can be achieved in patients with acute, severe hyponatraemia without the use of hypertonic saline. Indeed, present studies show that with V2RA, diuresis does not begin to increase before 1–2 h.

In all the studies published with V2RA, patients with hyponatraemia secondary to SIADH responded better than patients with chronic heart failure or cirrhosis.

In SIADH, around 15% of the treated patients do not significantly increase their SNa. The reason for this has not been studied. One cause is patients presenting a ‘reset osmotat’ [16]. These patients increase their EFWC but also increase their ADH secretion and their fluid intake when SNa increase, which contributes to decrease again SNa (personal observation, unpublished data). Another recently described cause of resistance to V2RA in adult patients is hyponatraemia secondary to nephrogenic syndrome of inappropriate antiurea (these patients are successfully treated with urea) [17]. Indications other than euvoletic or hypervolemic hyponatraemia for the use of V2RA are currently in development: retardation of progressive renal failure in polycystic kidney disease [18], V2R rescue therapy in congenital nephrogenic diabetes insipidus [19] and in the treatment of diabetic nephropathy, but other indications will probably also emerge.

Vaptans are a new class of oral vasopressin antagonists that will help in the management of most hyponatraemic patients.

Conflict of interest statement. GD has been a trialist for studies on Conivaptan, Lexivaptan, Tolvaptan and Satavaptan.

References

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Table 1. Treatments of hyponatraemia secondary to SIADH

<table>
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<th>Treatment</th>
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<tr>
<td>Water restriction combined with a high salt and protein intake (source of urea).</td>
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<td>Inhibition of pituitary ADH secretion:</td>
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<td>- Diphenhydantoin (rarely effective)</td>
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<td>- Niravoline (K-opioid agonist E) (non in development)</td>
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<td>ADH antagonists on the collecting tubule:</td>
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