NEW WEAPONS FOR MANAGEMENT OF HYPONATREMIA: VAPTANS

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Understanding of the dysnatremias and hence its treatment is a challenge to most of the physicians despite being the most common electrolyte disorders in hospitalized patients. The reason behind such complexity is that, unlike other substances change in plasma sodium concentration [Na+]p is not just affected by the change in mass balance (i.e. total body content) of sodium but also by changes in mass balance of potassium and total body water.

WATER HOMEOSTASIS & ROLE OF VASOPRESSIN

Water homeostasis involves regulation of water intake and water excretion. While water intake is regulated by regulation of thirst water excretion is regulated by kidneys through the presence or absence of vasopressin. Vasopressin (AVP) is the main hormone involved in the regulation of water homeostasis and osmolality of body fluids. In the case of osmoregulation, vasopressin secretion is relatively uncomplicated, with small decreases in osmolality causing a parallel decrease in vasopressin secretion and small increases in osmolality causing a parallel increase in vasopressin secretion. While the main effect if vasopressin is in the kidney a number of vasopressin receptors have been isolated from different organs which sub-serve different roles (Table 1).

Effect of vasopressin on kidneys:

In the kidney, water is conserved by the combined functions of the loop of Henle and the collecting duct. The loop of Henle generates a high osmolality in the renal medulla via the countercurrent multiplier system. Vasopressin acts in the collecting duct to increase water (and urea) permeability, thereby allowing osmotic equilibration between the urine and the hypertonic medullary interstitium. The net effect of this process is to extract water from the urine into the medullary interstitial blood vessels (vasa recta), resulting in increased urine concentration and decreased urine volume (antidiuresis). Vasopressin produces antidiuresis by its effects on the epithelial principal cells of the collecting tubule, which possess vasopressin receptors of the V2 type.

CLINICAL CLASSIFICATION OF HYPONATREMIA

A patient with hyponatremia can on fluid status be classified as having:

Low-volume hyponatremia: Occurs in conditions with renal or extrarenal loss of water and sodium with disproportionate loss of sodium.

High-volume hyponatremia: Occurs, in conditions with high extracellular volume but low effective

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<thead>
<tr>
<th>Subtype</th>
<th>Location</th>
<th>Function</th>
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<tr>
<td>V$_{1A}$ (vascular)</td>
<td>Vascular smooth muscle, liver, kidneys, reproductive organs, spleen, adrenal cortex, and platelets.</td>
<td>vasoconstrictive, mitogenic, and possibly platelet aggregative and hypercoagulable actions</td>
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<tr>
<td>V$_2$ (renal)</td>
<td>BL membranes of renal cortical and medullary collecting ducts and, also distal tubules</td>
<td>plasma tonicity, volume regulation, and blood pressure maintenance</td>
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<td>V$<em>3$ (V$</em>{1B}$)</td>
<td>anterior pituitary and, to a lesser extent - brain, kidney, pancreas, adrenal medulla</td>
<td>adrenocorticotropic hormone and ß-endorphin release</td>
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circulating blood volume resulting in enhanced thirst and water intake and hence excess water retention. Etiological conditions include congestive heart failure, nephrotic syndrome and chronic liver disease.

Normal-volume hyponatremia: Occurs when total body sodium is normal but there is increase in total body water. Etiological conditions include psychogenic polydipsia, hypothyroidism, glucocorticoid deficiency and syndrome of inappropriate ADH secretion.

VASOPRESSIN RECEPTOR ANTAGONISTS:

Initial investigations were carried out using peptide analogs of AVP receptor antagonists. But chronic blockade of AVP receptors by peptide V,R antagonists did not show persistent aquaretics, and further research with these compounds was limited by poor oral bioavailability, short half-lives, partial agonism and species-specific activity. In order to overcome these shortcomings, non-peptide VRAs (called vaptans) were introduced, they showed sufficient oral bioavailability and also sustained aquaretic effects.

Following is the classification of vaptans depending on the receptor selectivity (Table 2).

Only those vaptans which inhibit the V2 receptors in the kidney are useful in the treatment of hyponatremia as they lead to increased excretion of water by the kidneys without accompanying increase in excretion of sodium. This process termed as aquaretics leads to increase in plasma sodium concentration. Since they lead to significant water loss the vaptans are to be used only in euvolemic and hypervolemic hyponatremias and not in hypovolemic hyponatremia. Administration of vaptans to healthy individuals increases sodium concentration with vaptan therapy. However there is a large inter-individual variation in the response of vasopressin stimulation to osmotic stimuli due to polygenetic variation in the osmotic threshold. This explains the large inter-individual variation in response to the vaptans.

Clinical use of vaptans:

Currently vaptans have a role in treatment of chronic hyponatremia especially those associated with cirrhosis of liver, syndrome of inappropriate ADH secretion (SIADH), and congestive heart failure.

Vaptans in cirrhosis of liver:

Persistent vasopressin release due to nonosmotic stimuli like angiotensin II underlies the mechanism of water retention and hyponatremia in cirrhosis and this is the rationale behind using vasopressin receptor antagonists for hyponatremia in cirrhotic patients. Decaux described the effect of lixivaptan in 5 such patients whose mean serum Na rose from 128 to 133 mmol/L over a 72-hour period on 50 to 100 mg bid of the drug.7 A retrospective analysis to study the effect of intravenous conivaptan in 18 cirrhotic patients with hyponatremia after 72 hours of injection revealed that those patients who had lower baseline sodium and higher estimated GFR showed greater improvement in hyponatremia.8 Genes et al enrolled 110 participants with cirrhosis and hyponatremia (mean baseline plasma sodium 127 ± 5 mmol/l) in a randomized controlled trial in which the participants were treated with fluid restriction (1.5 L per day) plus placebo or three fixed doses of satavaptan (5.0 mg, 12.5 mg or 25.0 mg once daily) for up to 14 days. Over a period of seven days 54-64% of patients normalized plasma sodium concentrations or increased them by >5 mmol/l, and two patients (2.3%) developed hypernatremia, albeit without neurologic sequelae. No drug-related adverse events, other than increased thirst which was dose-related, occurred. In cirrhosis, the duration of vaptan action could also be longer owing to decreased hepatic clearance.

Vaptans in SIADH:

Soupart et al studied the effects of oral satavaptan in euvolemic hyponatremia attributed to SIADH. When combined with fluid restriction (1.5 L per day), both 25 mg and 50 mg of satavaptan produced increases in free water clearance and plasma sodium on day 1 that exceeded the changes in the placebo-treated group and were as large as those produced by 40 mg and 80 mg of intravenous conivaptan. Mean plasma sodium levels continued to rise gradually, and the aquaretics decreased only slightly during the next 72 h of satavaptan treatment. In another study using 40 and 80 mg of i.v conivaptan it was observed that though the serum sodium increased within 24 hours, the aquaretic effects started declining by 72 hours. Thus satavaptan was more effective in sustaining aquaretics compared to conivaptan in patients with SIADH. These variations may be attributed partly to the different routes of administration (intravenous versus oral) and/or rates of clearance of the two vaptans. However, they could also reflect smaller increases in plasma vasopressin levels in the satavaptan study. The persistent efficacy of satavaptan was also evident in an open label follow-up trial of 23 days to 12 months which minimized or prevented recurrence of hyponatremia in most study participants.

Vaptans in congestive heart failure:

Gheorghiade, M. etal in a double blind randomized controlled

| Table 2: Various vaptans in research & clinical use |
|---------------------------------|----------------|----------------|----------------|----------------|
| Unselective (mixed V1a/V2)     | V1a selective | V1b selective | V2 selective   |                  |
| Conivaptan                     | Relcovaptan  | Nelivaptan    | Mozavaptan     | Tolvaptan       |
| Mozavaptan                     | Satavaptan   | Tolvaptan     | Tolvaptan      | Tolvaptan       |

The table above lists various vaptans in research and clinical use for hyponatremia, including their selectivity and concentration. It highlights the importance of choosing the right vaptan based on the patient’s condition and the desired outcome.
trial studied 254 patients with class II or III CHF. The patients were randomized into four study groups to receive placebo, 30, 45, or 60 mg of tolvaptan daily for 25 days, while being maintained on furosemide, but not water restricted. The patients on all doses of the vasopressin antagonist lost weight (approximately 1 kg) and maintained it throughout the duration of the study. The serum Na rose by 3 mmol/L in the first 24 hours, but returned to baseline subsequently. 28% of the patients were hyponatremic (serum Na<136 mmol/L) and among the patients who were hyponatremic at baseline, 80% of those on tolvaptan versus 40% of those on placebo normalized their serum Na within 1 day and maintained it throughout the duration of the study. The mean increase in plasma sodium concentration after the first dose of tolvaptan in a subset of 20 patients with hyponatremia was slightly larger (5 mmol/L) than in the group as a whole and was similar to that observed in healthy adults given the same doses of tolvaptan and allowed to drink ad libitum.

In a subsequent study, the same group examined the effects of 30, 60, or 90 mg of tolvaptan in 319 hospitalized patients with CHF and ejection fractions <40%. Patients on active drug had greater in-hospital weight loss than those on placebo. In the hyponatremic patients, the changes in serum Na were similar to those of the previous study. A post hoc analysis revealed a trend towards a decrease in mortality in the subgroup with renal insufficiency and more severe CHF.

Another randomized controlled study evaluated the acute effects of five different doses (10-400 mg) of lixivaptan in patients with New York Heart Association class III congestive heart failure and normal or low serum sodium levels. The endpoint was renal effects of lixivaptan at 24 hours. Compared with placebo, doses of lixivaptan >10 mg produced variable increases in urine flow and free water clearance, 2-4 h after treatment. At higher doses (150-400 mg), the increased water excretion was associated with a statistically significant rise in levels of serum sodium (of unspecified magnitude) and plasma vasopressin. However they did not study the effect on hyponatremic symptoms. No serious adverse events were linked specifically to the treatment.

Two additional studies evaluated the effects of tolvaptan on cardiac function and survival in patients with congestive heart failure. The ACTIV in CHF study was a phase II study conducted to assess the acute and chronic effects of varying doses of tolvaptan in patients with worsening CHF requiring hospitalization. In about 45 of 68 hospitalized patients with hyponatremia the plasma sodium increased by at least 2 mmol/l during treatment with 30 mg, 60 mg or 90 mg doses of tolvaptan. These patients also had a lower mortality rate (11%) 60 days after discharge as compared to patients whose hyponatremia did not improve (22%). This finding suggests that correction of hyponatremia in congestive failure improves the poor outcome with which it is otherwise associated.

In the EVEREST study treatment with 30 mg daily of tolvaptan for 60 days raised plasma sodium levels and improved some secondary measures of cardiac function in patients with acute heart failure and normal or low plasma sodium concentration but did not affect mortality or morbidity compared with placebo. Thus, the major benefits of vaptan therapy seem to be limited to patients with hyponatremia. Thus to summarize the role of vaptans in CHF:

1. Vaptans in addition to standard therapy produced rapid and sustained decreases in body weight during hospitalization.
2. There was no apparent dose response with the doses tested in the studies.
3. Tolvaptan was associated with normalization of serum sodium in patients with hyponatremia.
4. Compared with placebo, use of tolvaptan was not associated with any significant difference in worsening heart failure at 60 days (eg, with regard to rates of death, rehospitalization, and unscheduled visits for CHF).
5. There was a trend toward lower mortality with tolvaptan in patients with clinical congestion, hyponatremia, or abnormal renal function.

Are Vaptans safe?

Though vaptans have definite place in the treatment of hypervolemic and euvoolemic hyponatremia there are some safety concerns. This is because in many of the above trials it was observed that the hyponatremia correction occurred was faster than that recommended and there is no guideline for back titration of the sodium correction once overcorrection has occurred. However no case of osmotic demyelination syndrome has been reported with the use of vaptans. However more studies are required to determine the optimal dosing, frequency of monitoring and precautions to be taken while a patient is on vaptans.

However following are the important adverse effects of vaptans:

- Intravenous conivaptan is associated with inflammation at infusion sites
- Oral tolvaptan has been associated with increased incidence of gastrointestinal bleeding in patients with liver diseases. Hence this drug is usually avoided in patients with liver disease and portal hypertension.

It is also important to remember that vaptans are not to be used in the following types of hyponatremia:

- Hypovolemic hyponatremia (As vaptans can cause hemodynamic instability)
- Euvolemic hyponatremia caused by emetic stimuli or
adrenal insufficiency (Vaptans are not necessary)

- Syndrome of inappropriate diuresis caused by activating mutation in vasopressin receptor (As vaptans are ineffective)

CONCLUSIONS

Vaptans are the newest and the most promising drugs in the management of chronic euvoletic and hypervolemic hyponatremia but not to be used for acute symptomatic hyponatremia where 3% saline is the treatment of choice. Vaptans are proven to be safe and effective in most of the trials but it has to be remembered that its effects are often short lasting and shows large interindividual variation. Vaptans are at present most invaluable for hypervolemic hyponatremia where the correction of hyponatremia has effects on long term survival.

REFERENCES

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