A Case of Effective Correction of SIADH with Low Dose Tolvaptan: No Trade off for an Economic Benefit

Ruth Casey1,*, Michelle Canavan1, Michael Dennedy1, Paula O Shea1, Sylvia Blaskova2 and Marcia Bell1

1Department of Endocrinology, Galway University Hospital, Galway, Ireland
2Department of Clinical Biochemistry, Galway University Hospital, Galway, Ireland
3Department of Oncology, Galway University Hospital, Galway, Ireland

Received Date: April 22, 2015, Accepted Date: September 05, 2015, Published Date: September 10, 2015.

*Corresponding author: Ruth Casey, Department of Endocrinology, Galway University Hospital, Galway, Ireland, E-mail: ruthcasey232@gmail.com

Abstract

Hyponatremia is a common electrolyte abnormality in the hospital setting and can cause significant morbidity and mortality. Syndrome of anti diuretic hormone (SIADH) secretion can pose management difficulties particularly if the etiology is not easily reversed. Fluid restriction as a treatment option is complicated in the acutely unwell patient, and fluid restriction is of limited treatment value once urine osmolarity exceeds 500 mosmo/kg. The “Vaptan” class of drugs has provided another therapeutic option in the management of euvolemic hyponatremia secondary to SIAD. The therapeutic use of this drug is sometimes limited by the associated expense of the drug. We present the case of a patient who was successfully treated with Tolvaptan for SIAD using a reduced dose, highlighting the role of dose reduction of Tolvaptan as an effective therapeutic option for SIAD with an associated economic benefit.

Keywords: Hyponatremia; SIADH; Tolvaptan

Case Report

We present the case of a 71 year old, retired farmer who presented to the Emergency Department in July 2014 with cough and un-steadiness on his feet.

The patient described a three-week history of cough productive of green sputum and occasional specks of blood. He was a smoker, smoking 15 cigarettes per day and had a 40 pack smoking history. He denied any weight loss or night sweats and there was no family history of oncological disease.

His chest x-ray on admission revealed a right lower lobe consolidation and a small right pleural effusion. His biochemical investigations revealed a hyponatremia, with sodium of 120mmols/L. A diagnosis of syndrome of inappropriate antidiuresis (SIAD) was made on the basis of a euvolemic serum sodium status clinically, and biochemical indices (Table 1).

The volume status was based on observation of his jugular venous pressure, mucous membranes and blood pressure, which did not reveal a postural drop. A contrast CT of thorax was carried and revealed a 4.4 cm lobulated soft tissue mass in the right lower lobe and lymphadenopathy in the right hilar, sub-cardinal and paratracheal region bilaterally. A CT of brain revealed no abnormality and a staging CT did not demonstrate any distant metastases. An endobronchial biopsy was performed and histology confirmed a small cell carcinoma with immunohistochemical staining positive for TTF1 and CD56, consistent with a lung primary. Following an oncology review, four cycles of cisplatin and etoposide for limited stage small cell cancer of lung was planned. This chemotherapy regime would also involve a pre hydration phase with 3-4 liters of normal saline. As the patient remained hyponatremic the endocrine service was consulted. On review the patient was euvolemic and adhering to a strict fluid restriction of one liter a day. His fluid balance revealed that he had a negative fluid balance of 100 – 200 mls since he was commenced on a strict fluid restriction. His urine osmolality was 650 mmol/kg, indicating that the kidneys had limited extra concentrating ability and that fluid restriction was unlikely to improve the serum hyponatremia. The urine sodium was 81mmol/L, and there was no interfering medication on chart review. His only regular medications included aspirin and a proton pump inhibitor. The etiology of the inappropriate anti diuretic hormone was attributed to the small cell carcinoma of lung and as proton pump inhibitors can be implicated in SIAD, this medication was stopped. The concern was that the patient would require fluid with chemotherapy administration and therefore there was potential for worsening of the hyponatremia. The only clinical sign attributable to the hyponatremia was an unsteady gait, with no other evidence of cognitive or cerebellar dysfunction. Chemotherapy was commenced cautiously with close monitoring of sodium and fluid balance. The sodium remained between 126 and 128 mmols/L and the first cycle of chemotherapy was completed and the patient was discharged with arrangements to return to the day ward for the second cycle of chemotherapy.

The patient was electively admitted two weeks later for his second cycle of chemotherapy. Routine bloods revealed deterioration in the hyponatremia with sodium of 117mmols/L. Clinical examination again revealed an unsteady gait. As a result the elective chemotherapy was postponed and the patient was admitted for further management of hyponatremia. The endocrine service was again consulted and in light of the worsening hyponatremia and need for further chemotherapy, the decision was made to commence democycline. However the patient became clinically and biochemically dehydrated on 150mg twice daily of democycline, despite an improvement in his sodium and as a result this was discontinued. On review of the case, a decision was made to apply to pharmacy for tolvaptan for treatment of chronic SIADH.

---

Table 1: Serum investigations on admission.

<table>
<thead>
<tr>
<th>Serum investigations</th>
<th>Result</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na</td>
<td>120mmols/L</td>
<td>(132-146)</td>
</tr>
<tr>
<td>K</td>
<td>4.3 mmols/L</td>
<td>(3.7-5.4)</td>
</tr>
<tr>
<td>Urea</td>
<td>6.3 umol/L</td>
<td>(2.9-8.2)</td>
</tr>
<tr>
<td>Creatinine</td>
<td>66 umol/L</td>
<td>(64-104)</td>
</tr>
<tr>
<td>Free thyroxine</td>
<td>21.0 pmol/L</td>
<td>(10.5-22)</td>
</tr>
<tr>
<td>Thyroid stimulating hormone</td>
<td>0.56 mIU/L</td>
<td>(0.27-4.2)</td>
</tr>
<tr>
<td>Cortisol</td>
<td>735 mmol/L</td>
<td></td>
</tr>
<tr>
<td>Serum osmolarity</td>
<td>251 mOsmol/L</td>
<td>(280-301)</td>
</tr>
<tr>
<td>HbA1c</td>
<td>48 mmol/L</td>
<td>(20-42)</td>
</tr>
</tbody>
</table>
The patient was initially commenced on an off-licence, half dose of tolvaptan at 7.5mg a day with gradual improvement of sodium levels. In the interim the patient had a re-staging CT which indicated no therapeutic response. The chemotherapy regime was switched to second line irinotecan and carboplatin. The sodium levels returned to normal and the patient was discharged on tolvaptan 7.5 mg daily with close electrolyte review. The patient has now completed two cycles of irinotecan and carboplatin and his sodium levels have remained in the normal range. There has been no further delay or cancellation of chemotherapy and the most recent CT indicates a therapeutic response in terms of the size of the mediastinal adenopathy and right lower lobe mass. The dose of tolvaptan was reduced after four months of therapy and he is now maintained on 3.75mg of tolvaptan with sodium remaining with the normal range at 136 mmols/l. The patient was continued on a one and a half liter fluid restriction on discharge with the hope of weaning the Tolvaptan completely. Dietary sodium intake was assessed by a dietician and felt to be adequate, ruling out the need for supplementation with sodium tablets. Importantly the patient does describe an improved quality of life with improved energy, cognition and gait with the sodium now within normal range.

Discussion

Hyponatremia is the most commonly encountered electrolyte abnormality [1] and SIAD is the leading cause of hyponatremia in hospitalized patients [2]. Despite the prevalence of SIAD, its management remains complex and controversial.

Tolvaptan is a novel treatment administered orally. It is a selective non-peptide arginine vasopressin (AVP) receptor (AVPR) antagonist that blocks binding of AVP to V2 receptors in the distal nephron, allowing an electrolyte-free water excretion, without significantly affecting renal sodium and potassium excretion, thus remedying the anti-diuresis effect of inappropriate ADH production[3]. At present Tolvaptan is licensed at a starting dose of 15mg and a maximum dose of 60mg for the treatment of euvolemic and hypervolemic hyponatremia but initiation of treatment must be within a hospital setting. The safety and efficacy of tolvaptan in euvolemic hyponatremia was verified by the SALT-1 and SALT-2 trials [4]. The recommended starting dose is 15mg and the cost per tablet is 88 euro in Ireland. The economical benefit of tolvaptan was evaluated based on the patients enrolled in the SALT-1 and SALT-2 trials [5]. In this study a cost-offset model was utilized to determine the impact of tolvaptan on hospital cost and length of hospital stay. The findings of this study were that tolvaptan was associated with a shorter hospital stay compared to placebo and even accounting for drug cost, there was an overall saving in the tolvaptan arm of $694 per admission. We also know from previously published cases, that a lower dose of tolvaptan can be effective in rectifying hyponatremia due to SIAD [6]. A recent case series has also confirmed the efficacy of low dose tolvaptan in the effective treatment of SIAD in a cohort of oncology patients [7].

This case highlights the complex management of SIAD and the delay in treatment that can occur in SIAD associated with oncological disease. Importantly it also confirms that eunatremia can be achieved and maintained with a lower dose of tolvaptan then previously recommended adding to the growing evidence base to support low dose vaptan to achieve cure of SIAD with improved economic benefit.

References


*Corresponding author: Ruth Casey, Department of Endocrinology, Galway University Hospital, Galway, Ireland, E-mail: ruthcasey232@gmail.com

Received Date: April 22, 2015, Accepted Date: September 05, 2015, Published Date: September 10, 2015.

Copyright: © 2015 Ruth Casey et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.