The use of a specific protocol for initiation of tolvaptan therapy in mild/moderate euvelomic hyponatremia secondary to SIADH: not a single case of overcorrection

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**OBJECTIVES**

The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is the most common cause of hyponatremia (serum sodium <135 mmol/L) in clinical practice. The use of oral Tolvaptan (TV) for treatment of this condition has been shown to be safe and effective in well-designed, randomized clinical trials 1, 2. The ESE guideline 3 states a risk for overcorrection of serum sodium levels (SNas) with TV, thus increasing the possibility of developing Osmotic Dehydration Syndrome (ODS). The recommended initial dose of Tolvaptan is 7.5 mg, although some physicians use 7.5 mg the first day to reduce the potential risk of serum sodium overcorrection. We had previously reported our preliminary data in 7 patients 4, indicating that an initial dose of 7.5 mg of Tolvaptan was safe and effective in SIADH in this small group of patients. Our current protocol does not only include an initial dose of 7.5 mg, but also measures to brake the Serum Sodium rise on day 1 when necessary. Our aim was to evaluate the effectiveness and safety of our protocol.

**METHODS**

This single centre, retrospective study included 86 patients with mild or moderate hyponatremia due to SIADH, treated between 2011 and 2015 in the Hospital Clínico San Carlos Hospital in Madrid, Spain. TV was either administered during conventional hospitalization or under supervision in our Endocrine Day Hospital. The protocol includes baseline assessment, as well as 24, 48 and 60 hours following the initial 7.5 mg dose of TV: Serum glucose, creatinine, urea, sodium corrected for total proteins and dyes, plasma osmolality, urine sodium and osmolality were determined. Overcorrection was defined as a SNas rise over 10 mmol/L in 24 hours or over 18 mmol/L in 48 hours. In patients at risk for development of ODS (malnutrition, hypocalcaemia, alcoholism, liver disease), overcorrection was defined as a SNas rise over 8 mmol/L in any 24-hour period, during the first 48 hours following initiation of therapy. Statistical analysis was performed using SPSS software statistics 21, with Student’s T test, X², and Spearman’s Rho. Na in mmol/L. Osm in mOsm/Kg

**RESULTS**

**SEX**

<table>
<thead>
<tr>
<th>MALE</th>
<th>FEMALE</th>
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<td>51.6%</td>
<td>48.4%</td>
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**PLACE OF TREATMENT**

- DAY HOSPITAL: 76.73%
- Conventional Hospital: 23.27%

**ETIOLOGY**

- Neurological: 13.95%
- Ectopic: 29.07%
- Pharmacological: 10.43%
- Diabetic or the Older: 16.55%
- Others: 27.98%

**NADIR SERUM SODIUM**

120.53 (SD 6.27) mmol/L

**BASELINE CHARACTERISTICS**

- Serum Sodium: 128.24 (SD 4.14) mmol/L
- Plasma osmolality: 266.43 (SD 9.16) mOsm/Kg
- Urine osmolality: 450.1 (SD 153.32) mOsm/Kg
- Spot Urine sodium: 65.18 (SD 44.26) mmol/L
- Serum Urine Acid Concentration: 3.07 (SD 1.43) mg/dL
- Creatinine: 0.67 (SD 0.23) mg/dL
- Furst formula: 0.92 (SD 0.36)

**DEPICTION OF OUR SPECIFIC PROTOCOL FOR INITIATION OF TOLVAPTAN IN MILD OR MODERATE HYPONATREMIA DUE TO SIADH**

- **DAY 1**
  - TOLVAPTAN (TV) 7.5 mg Ad libitum oral fluid intake
  - 6 h post TV
  - Na ascent > 4 mmol/L
  - Na ascent < 5 mmol/L

- **DAY 2**
  - 24 h post TV
  - Treatment to prevent overcorrection (TPD)
  - Na ascent > 10 mmol/L (x 8 mmol/L, Risk of ODS)
  - No TPO TV 15 mg
  - Repeat Na in 4 h
  - Na ascent > 10 mmol/L (x 8 mmol/L, Risk of ODS)
  - TPO TV 7.5 mg
  - No TPO TV 7.5 mg
  - 6 h post TV
  - 3 mcg DOCA/KG SC
  - 7 mcg DOCA/KG SC

- **DAY 3**
  - 48 h post TV
  - Na ascent 24 to 48 h
  - 5 mmol/L, Assess adequate oral fluid intake
  - 6 mmol/L, 5% Dextrose 3 mL/kg 1 hour
  - 7 mmol/L, 5% Dextrose 3 mL/kg 1 hour

**CONCLUSION**

- Our specific protocol for initiation of TV in mild or moderate SIADH-induced hyponatremia is safe and effective. There was not a single case of overcorrection of the serum sodium in our patients. No patient developed ODS.
- Almost half of the patients presented a normal serum sodium concentration 48 hours after initiation of TV therapy.
- We must improve patients’ fluid intake at our Endocrine Day Hospital.

**REFERENCES**

4. St. Cuesta et al. An initial dose of 7.5 mg Tolvaptan is safe and effective in the treatment of hyponatremia caused by SIADH. Endocrine Abstracts (2012-23) P1169