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

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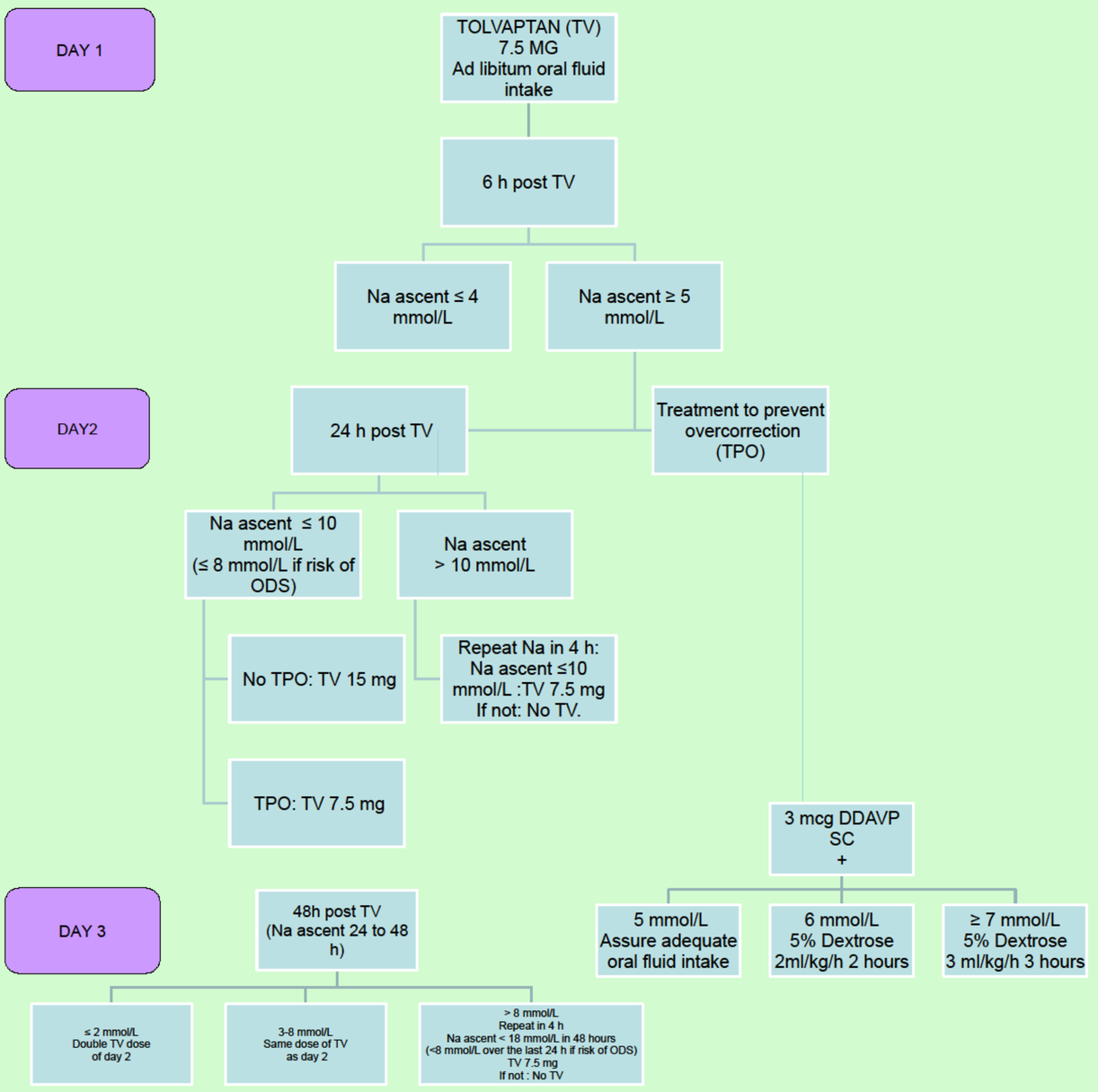
OBJETIVES

The syndrome of innapropriate 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 (SNa) with vaptans, thus increasing the possibility of developing the Osmotic Demyelination Syndrome (ODS). The recommended initial dose of Tolvaptan is 15 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 inital 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

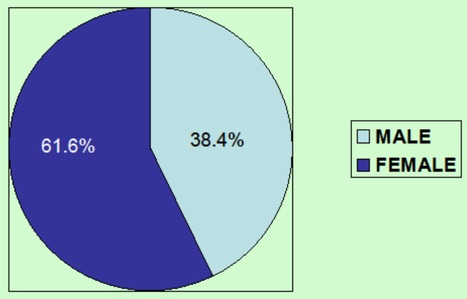
This single centre, retrospective study included 86 patients with mild or moderate hyponatremia due to SIADH, treated between 2011 and 2015 in the Hospital Clínico San Carlos Hospital in Madrid, Spain. TV was either administered during conventional hospitalization or under supervision in our Endocrine Day Hospital. The protocol includes baseline assessment , as well as 6, 24 and 48 hours following the initial 7.5 mg dose of TV: Serum glucose, creatinine, urea, sodium corrected for total proteins and glycemia, plasma osmolarity, urine sodium and osmolarity were determined. Overcorrection was defined as a SNa rise over 10 mmol/L in 24 hours or over 18 mmol/L in 48 hours. In patients at risk for development of ODS (malnutricion, hipocalemia, alcoholism, liver disease), overcorrection was defined as a SNa rise over 8 mmol/L in any 24-hour period, during the first 48 hours following initiation of therapy. Statistic analysis was performed using SPSS software statistics 21, with Student's T test, X^2, and Spearman's Rho. Na in mmol/L. Osm in mOsm/Kg

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

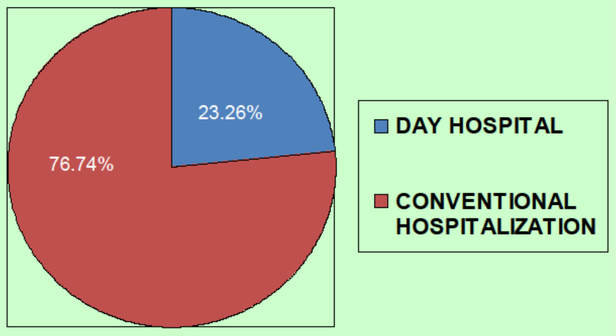


RESULTS

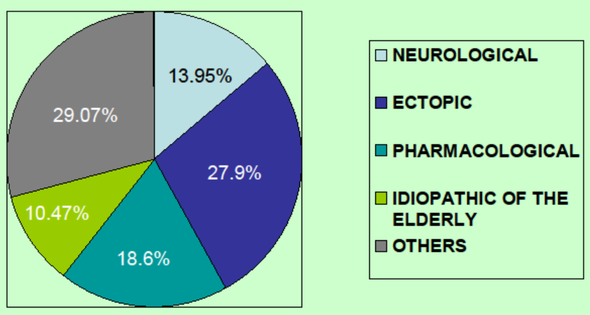
SEX



PLACE OF TREATMENT



ETIOLOGY



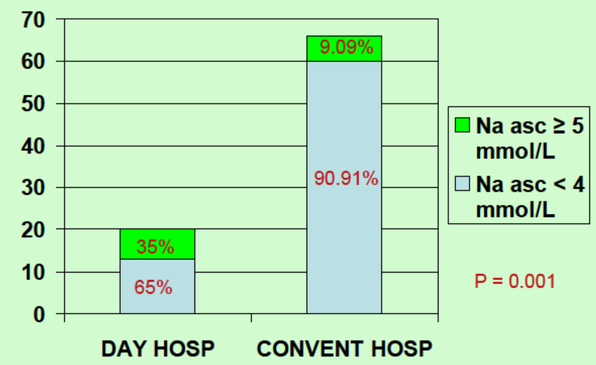
NADIR SERUM SODIUM
120.53 (SD 6.27) mmol/L

BASALINE CHARACTERISTICS

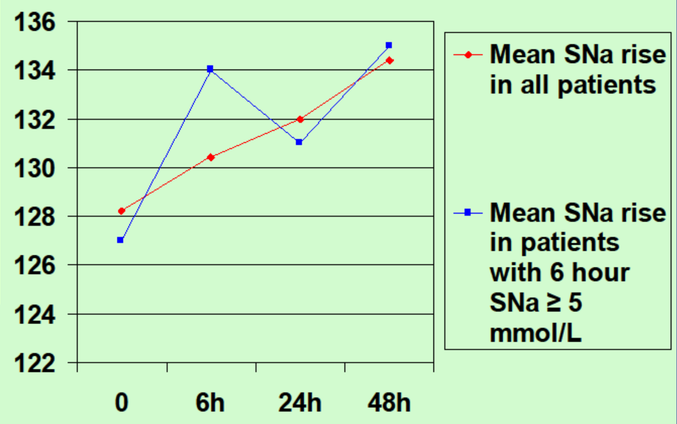
Serum Sodium	128.24 (SD 4.14) mmol/L
Plasma osmolarity	266.43 (SD 9.16) mOsm/Kg
Urine osmolarity	450.1 (SD 153.32) mOsm/Kg
Spot Urine sodium	85.18 (SD 44.28) mmol/L
Serum Uric Acid Concentration	3.07(SD 1.43) mg/dl
Creatinine	0.67 (SD 0.23) mg/dl
Furst formula	0.92 (SD 0.36)

- 42/86 (48%) patients had 48-hour a serum sodium above 135 mmol/L.
- Serum Na rise≥ 5 mmol/L, 6 hours postTV, occurred in 13/86 (15.1%) and it was significantly associated with:
  - Therapy in the Endocrine Day Hospital p=0.001
  - Lower basal serum sodium R= -0.292, p= 0.006
  - Lower basal uric acid concentration R= -0.382 p= 0.005
- **Not a single patient presented overcorrection of SNa levels 24 h or 48 hours following initiation of therapy.**
- The maximum 24-hour serum sodium rise over the first 24 hours following the initial dose was 10 mmol/L in two patients; whereas one patient corrected 15 mmol/L in the first 48 hours.
- 10% of patients did not respond to the initial 7,5 mg dose of TV, yet did respond to the 15 mg dose.
- Side effects
  - Two patients referred intense thirst.
  - -- **No patient developed ODS**.

SERUM Na RISE AND PLACE OF TREATMENT



MEAN RISE IN SNa IN ALL PATIENTS AND IN PATIENTS WITH 6-HOUR SNa RISE ≥ 5 MMOL/L.



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.

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