EFFICACY AND SAFETY OF TOLVAPTAN IN TREATING SEVERE HYPONATREMIA DUE TO SYNDROME OF INAPPROPRIATE SECRETION OF ANTIDIURETIC HORMONE (SIADH)

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INTRODUCTION

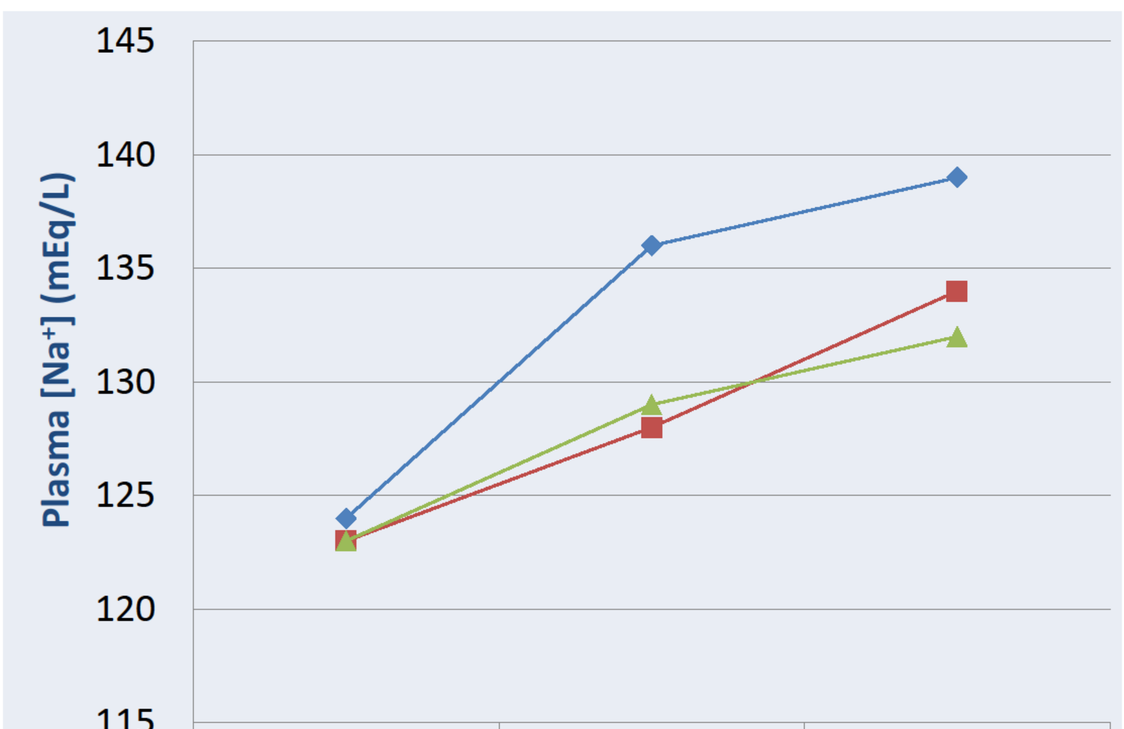
Tolvaptan is an oral antagonist of V2-receptors for ADH that has been demonstrated to be really efficient in treating hyponatremia due to SIADH. Its safety and efficacy, however, have been validated only for mild degrees of hyponatremia and there is still uncertainty about its use in more severe degrees of this condition, especially in those cases where hyponatremia is extremely symptomatic and the infusion of hypertonic solution remains the mainstay of treatment. The aim of this study is to analyze our experience in treating such patients with tolvaptan.

MATERIALS AND METHODS

We retrospectively analyzed clinical and biochemical data following the administration of Tolvaptan in three patients with severe hyponatremia. All patients were euvolemic and had elevated natriuresis without signs of adrenal or thyroid dysfunction, all criteria consistent with diagnosis of SIADH (Table 1). In all patients, hyponatremia proved to be resistant to the infusion of hypertonic solution before the administration of Tolvaptan. The administered daily dose of 15 mg was continued for several months in order to prevent relapses.

RESULTS

Serum sodium increased by 5, 12 and 6 mEq/L in 24 hours, in each patient respectively, and further increased in 48 hours (Figure 1). All clinical and laboratory data are listed in Table 2. Correction of serum sodium led to remission of symptoms in all patients and all the weaning attempts from the drug resulted in symptoms relapse. Therefore, it has been a long period since these patients have started this therapy, and during this time it appeared to be both necessary for the control of natremia and well tolerated. The only side effect reported was a slight decompensation of the already known diabetes mellitus in patient 2, which is a known side effect reported by the manufacturer.



	Baseline	24 Hours	48 Hours
Patient 1	124	136	139
Patient 2	123	128	134
Patient 3	123	129	132

FIGURE 1 – Diagram showing changes in plasma sodium concentration (Y axis) following the administration of Tolvaptan

DISCUSSION

To the best of our knowledge, this is the first report of a long-standing therapy with Tolvaptan in patients who were symptomatic for severe hyponatremia due to SIADH. Treatment of severe hyponatremia is challenging for the risk of myelinolysis and the most cautious method is the infusion of hypertonic solution with continuous monitoring of sodium levels. Drawbacks of oral therapy with Tolvaptan are a hypothetical uncontrolled increase of natremia and the yet undiscovered long-term safety. In our series, however, the dose chosen allowed to increase sodium concentration in a safe way (i.e. less than 12 meq/L in 24 hours) and appeared to be well tolerated in the long-term, with a marked improvement in quality of life. Our experience needs to be confirmed by larger randomized clinical trials.

SIADH Diagnostic Criteria
Non-diluitional hyponatremia (Na+ < 135 mmol/L)
Low serum osmolarity (< 280 mOsm/L)
Increased natriuresis (>40 mmol/L)
Clinical euvolemia
Normal thryoid and adrenal function

TABLE 1 – Diagnostic Criteria for SIADH

Patient	SIADH Cause	Symptoms	Follow-Up Time	Adverse Drug Reactions
1	Meningitis	Coma	20 months	None
2	Metastatic Reninoma	Dizziness, headache and confusion	12 months	Slight decompensation of diabetes
3	Not Determined	Psychiatric disturbances and lower limbs weakness	8 months	None

TABLE 2 – Clinical and Laboratory data of the three patients treated with Tolvaptan

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Acid-base / Electrolytes / Nephrolithiasis
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DOI: 10.3252/pso.eu.50era.2013
Poster presented at: ERA-EDTA 50th Congress Istanbul, Turkey May 15-21, 2013
PosterSessionOnline.com