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Letters to the Editor

Clinical experience with different initial doses of tolvaptan in SIADH☆

Experiencia clínica con distintas dosis iniciales de tolvaptan en siadh

Dear Editor,

Hyponatraemia, defined as the decrease in serum sodium concentration below 135 mmol/l, is the most prevalent electrolyte disorder in the hospital environment, presenting a prevalence of 15–30 % at admission,[1] being associated with an increase in hospital stay and mortality.[2]

SIADH constitutes the leading cause of hyponatraemia in hospitalised patients.[3] Pathophysiologically it is caused by an inability to suppress vasopressin secretion, resulting in a reduction in urinary volume and concentration, leading to the decrease in serum natraemia (SNa). The introduction of vaptans, antagonists of vasopressin V2 receptors, has been the main therapeutic novelty in its management, with tolvaptan available in Europe.[4] Although the lowest formally accepted dose is 15 mg/day, the risk of overcorrection sometimes leads to an initial dose of 7.5 mg/day.

As with any treatment of hyponatraemia, the main concern is the rapid overcorrection of natraemia levels, which can possibly cause life-threatening osmotic demyelination.[5] To try to avoid it, a close and individualized monitoring of SNa should be performed in the first hours of initiation of treatment, marking as increase limit targets 8–12 mmol/l at 24 h and 12–18 mmol/l at 48 h.[6–8]

We assessed the use of tolvaptan in a tertiary hospital between March 2014 and August 2017, in order to provide knowledge regarding the use of tolvaptan. During this period 17 patients received treatment with tolvaptan. Different starting dosages were used (7.5 mg; 15 mg; 30 mg). Treatment with a dose of 7.5 mg was started on 9/17 patients. Table 1 summarises the characteristics by groups. 100 % of the patients presented chronic hyponatraemia (> 48 h). 17.6 % presented natraemia < 120 mmol/l at the start of treatment.

The evolutionary follow-up of SNa was uneven, with an analytical determination being made at 6 h in 23.5 % (n = 4), at

Table 1 – General characteristics of the patients, broken down by initial dose of tolvaptan.

	7.5 mg	15 mg	30 mg	Total
n	9	7	1	17
Diagnosis, n (%)				
Idiopathic SIADH	1 (11.1)	0 (0)	0 (0)	1 (5.9)
Pharmacological SIADH	3 (33.3)	0 (0)	0 (0)	3 (17.7)
Postsurgical SIADH	0 (0)	3 (42.8)	0 (0)	3 (17.7)
Paraneoplastic SIADH	3 (33.3)	1 (14.3)		3 (17.7)
SIADH secondary to neurological disease	2 (22.2)	2 (28.6)	1 (100)	4 (23.5)
SIADH secondary to respiratory disease	1 (11.1)	1 (14.3)	0 (0)	2 (11.8)
Dilutional hyponatraemia (cirrhosis)	1 (11.1)	0 (0)	0 (0)	1 (5.9)
Age (years), mean (IQR)	73.0 (13.7)	65.9 (14.9)	59.0	70.9 (16.8)
Sex %, male/female	66.7/33.3	57.1/42.9	100/0	64.7/35.3
Cause for admission, n (%)				
Start of tolvaptan	1 (11.1)	0 (0)	0 (0)	1 (5.9)
Hyponatraemia	6 (66.7)	2 (28.6)	1 (100)	9 (52.9)
Other	2 (22.2)	5 (71.4)	0 (0)	7 (41.2)
Initial SNa (mmol/l), mean (IQR)	125 (6)	125 (4)	115	125 (6)

IQR: interquartile range; SIADH: syndrome of inappropriate antidiuretic hormone secretion; SNa: natraemia.

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Table 2 – Evolution of natraemia during follow-up after the start of tolvaptan in the group of patients.

		7.5 mg	15 mg	Total	p
Eunatraemia, %	6 h	0	0	0	–
	12 h	0	0	0	–
	24 h	25	25	33.33	–
	48 h	33.33	0	20	0.361
	72 h	50	66.67	57.14	0.513
Overcorrection, %	6 h	0	0	0	–
	12 h	0	0	0	–
	24 h	50	25	38.46	0.501
	48 h	0	0	0	–

Overcorrection is considered as increases > 5 mmol/l at 6 h; > 8 mmol at 12 h; > 10 mmol/l at 24 h; > 18 mmol/l at 48 h.

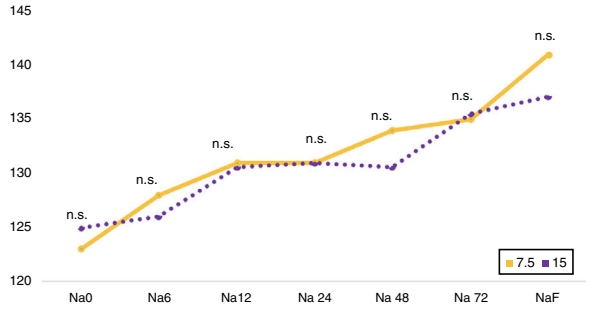

Fig. 1 – Comparison between starting doses of tolvaptan 7.5 and 15 mg. Line chart of the evolution of natraemia Na 0, Na 6, Na 12, Na 24, Na 48, Na 72, NaF, which correspond to the initial natraemia, at 6, 12, 24, 48 and 72 h, and the last available natraemia, respectively.
Na: natraemia; n.s.: not significant.

12 h in 29.4 % (n = 5), at 24 h in 76.5 % (n = 13), at 48 h in 70.6 % (n = 12) and at 72 h in 58.8 % (n = 10). A comparison (Fig. 1) was made of the evolution of SNa as a function of the starting dose of tolvaptan used (7.5 vs 15 mg), without significant differences in the different cut-off points.

Table 2 details the percentages of patients who achieved eunatraemia or presented overcorrection. No patient developed osmotic demyelination. No differences were found in the rate of overcorrection by starting dose used, sex, age or aetiological diagnosis. A trend to a higher rate of overcorrection (24 h) was observed in patients without SNa control at 6 h (0 vs 30 %; p = 0.279) and at initial SNa < 120 mmol/l (30 vs 66 %; p = 0.510), without statistical significance.

In our experience, there seems to be no differences in the evolution of natraemia in the first 72 h per starting dose of tolvaptan (7.5 vs 15 mg), and this issue should be assessed in new studies, given the inherent limitation of the small sample used. We found a high overcorrection rate at 24 h (38.5 %), higher than 5.6 % as published in the SALT-1 and SALT-2 studies[9] on the drug's safety. The explanation could come from the inclusion of patients with initial SNa < 120 mmol/l and the absence of follow-up of the evolution of SNa after the start of treatment, preventing the application of corrective measures. The variability in patient follow-up and the risks associated with an inadequate start of therapeutic management with tolvaptan show the need to follow the protocols recommended in the consensus of experts in the absence of specific studies on the subject.

Authorship

David E. Barajas-Galindo and Alfonso Vidal-Casariego conceived and designed the study. David E. Barajas-Galindo analysed the data and wrote the document. All authors contributed to the acquisition of data, to the writing of the manuscript and approved the final version thereof.

Conflict of interests

Dr Barajas-Galindo and Dr Gómez-Hoyos report that they have received fees from Otsuka Pharmaceutical Co. Ltd., outside of the work presented. All other authors declare that they have no conflicts of interest.

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David E. Barajas-Galindo[a,*], Alfonso Vidal-Casariego[a], Emilia Gómez-Hoyos[b], Paula Fernández-Martínez[a], María Guerra González[c], Ana Hernández-Moreno[a], Miran Alejo-Ramos[a], Rocío Villar-Taibo[a], Isidoro Cano-Rodríguez[a], María D. Ballesteros-Pomar[a]

[a] *Sección de Endocrinología y Nutrición, Complejo Asistencial Universitario de León, León, Spain*
[b] *Servicio de Endocrinología y Nutrición, Hospital Clínico Universitario, Valladolid, Spain*
[c] *Servicio de Farmacia Hospitalaria, Complejo Asistencial Universitario de León, León, Spain*

* Corresponding author.
E-mail address: dabarajas@saludcastillayleon.es (D.E. Barajas-Galindo).

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A reflection on screening for neoplasms in glomerulonephritis☆

Reflexion sobre el screenning de neoplasias en glomerulonefritis

Dear Editor,

We present the case of a 34-year-old man, a smoker, without a personal or family history of interest, who attended the emergency department with oedema of a week of evolution, presenting a nephrotic syndrome with: proteinuria of 15 g/24 h, with microhematuria, serum creatinine 0.9 mg/dl, eGFR > 60 ml/min/1.72 m^2 (MDRD), albumin 1.9 g/dl, cholesterol 557 mg/dl, leukocytes 5,500/μl (normal formula), haemoglobin 15.8 g/dl and 239,000/μl platelets.

He reported itching of during the last 2 months, so he took an antihistamine with a partial response. He had no skin lesions, and had no remarkable findings on physical examination.

In the complementary tests, the autoimmunity study was negative (anti-nuclear, anti-DNA, anti-neutrophil cytoplasm antibodies, antibodies against extractable nucleus antigens) and normal complement values. IgG levels were decreased: 393 mg/dl (normal range 700–1,600) with IgA and IgM values being normal, and a notable elevation of IgE levels : 565 IU/ml (< 100). The chest X-ray and abdominal ultrasound showed no pathological findings.

A renal biopsy was performed evidencing a minimal change disease.

Treatment was started with prednisone 60 mg/day obtaining a complete response 2 months after treatment (proteinuria 0.1 g/24 h) and starting a descending regimen thereafter. In the fifth month, while on 30 mg of prednisone, he suffered a relapse of the nephrotic syndrome (proteinuria 8 g/24 h), so the dose of prednisone was increased again to 60 mg/day with partial response at 2 months (proteinuria 0.6 g/24 h). In the descending regimen, with prednisone 40 mg/day, he relapsed again with proteinuria of 8.5 g/24 h, he was catalogued as a corticodependent and treatment with tacrolimus was started.

He was referred to the allergy department for the pruritus and high levels of IgE, and it was detected a cat hair allergy. He lived with multiple cats, so its causality with pruritus seemed reasonable, and he got rid of them.

The patient commented on the onset of atypical chest pain, which worsened with movements. The ECG showed no pathological changes. His wife attributed the pain it to the anxiety he had because of the clinical picture. Given the persistence of pain, he was assessed by cardiology and a stress test was performed that was clinically and electrically negative.

Given the increase in pain intensity, he went to the emergency department where they performed a CT scan to rule out pulmonary thromboembolism and pathological mediastinal adenopathies were detected.

Biopsy of the adenopathy showed classic nodular sclerosis Hodgkin lymphoma, stage II-A, with viral load of the Epstein-Barr virus (EBV) 11,200 IU/ml. He was treated with polychemotherapy (ABVD) and rituximab, with a very good response and a complete remission of lymphoma after the third cycle of chemotherapy, negativization of EBV and complete response of the nephrotic syndrome without the need for specific treatment. After one year of follow-up, the patient continues in complete remission of lymphoma and nephrotic syndrome.

The relationship of glomerulonephritis with a neoplastic process is well known. It was described for the first time in 1966,[1] and has been repeatedly confirmed over the years.[2,3] It often represents the first clinical manifestation of an underlying cancer. It has even been described that, sometimes, the neoplasia does not manifest itself until months or even years after the diagnosis of glomerulonephritis,[2,3] reasoning that a molecular phenomenon exists very early on in the neoplastic process.[4]

In a study that assessed 5594 patients with different forms of glomerulonephritis, there were found 911 neoplasms of

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