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Tolvaptan resistance is related with a short-term poor prognosis in patients with lung cancer and syndrome of inappropriate anti-diuresis

Articoli originali

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ABSTRACT

Purpose: Tolvaptan (TVP), a vasopressin receptor antagonist, represents a therapeutic option in the syndrome of inappropriate anti-diuresis (SIAD). The aim of this study was to evaluate the effect of TVP to treat and solve hyponatremia in oncologic patients.

Methods: 15 oncologic patients who developed SIAD have been enrolled. Patients receiving TVP belonged to group A, whereas group B was characterized by hyponatremic patients treated with hypertonic saline solutions and fluid restriction.

Results: In group A, the correction of serum sodium was achieved after 3.7±2.8 days. In group B, the target levels were obtained more slowly, after 5.2±3.1 days (p: 0.01) than in group A. The hospital stay and incidence of re-hospitalization were higher in group B than in group A. In this latter, 37% of patients had hyponatremic relapses, notwithstanding the progressive increase of doses from 7.5 to 60 mg per day of TVP, revealing a complete lack of response to TVP. In these patients, a growth of tumor mass or new metastatic lesions has been revealed.

Conclusion: TVP improved hyponatremia more efficiently and stably than hypertonic solutions and fluid restrictions. Positive consequences have been obtained about the rate of chemotherapeutical cycles concluded, hospital stay, rate of relapse of hyponatremia, and re-hospitalization.

Our study also suggested potential prognostic information that could be deduced from TVP patients, in whom sudden and progressive hyponatremia occurred, despite TVP dosage increase. A re-staging of these patients to rule out tumor mass growth or new metastatic lesions is suggested.

PAROLE CHIAVE: hyponatremia, paraneoplastic syndrome, syndrome of inappropriate anti-diuresis, tolvaptan, vasopressin

Introduction

The prognosis of oncologic patients is often related to the onset of electrolytic disorders, particularly if hyponatremia occurs [1]. The syndrome of inappropriate anti-diuresis (SIAD) represents the main cause of hyponatremia, even though differential diagnosis with concomitant comorbidities (heart failure, nephrotic syndrome, extracellular volume depletion, pulmonary disorders) and drugs (tricyclic antidepressants, selective serotonin reuptake inhibitors, opioids, chemotherapeutic agents and immunotherapy) needs to be carried out [2, 3].

In particular, SIAD is directly associated with malignancy as expression of a paraneoplastic endocrine effect mediated by an ectopic production of vasopressin (AVP) by cancer cells. Moreover, medications, particularly chemotherapic agents, such as vinca alkaloids, alkylating agents, and platinum compounds, which increase the AVP synthesis/release, could induce SIAD. Other drugs, such as cyclophosphamide, could enhance the water permeability of the distal tubule, in the absence of high AVP levels [1].

Fluid restriction remains the mainstay of treatment for acute and moderate hyponatremia associated with SIAD but inefficacy and frequent side effects, such as dehydration and acute kidney injury, often involving patients treated, at the same time with chemotherapy, require pharmacological interventions [4]. Demeclocycline, loop diuretics associated with sodium supplementation, and urea tablets could correct and solve hyponatremia [5]. In particular, the infusion of hypertonic saline (3%) is highly recommended in acute situations with neurological symptoms. The guidelines advise a bolus of 100–150 mL in 10 minutes, which might be repeated 2 to 3 times until serum sodium increase by 5 mmol avoiding overcorrection [6].

No more than 10 mmol in the first 24 hours or 8 mmol if there are risk factors must be reached in order to prevent severe damage to the central nervous system, such as central pontine myelinolysis, ultimately coma and death. The recommendation is to carry on the correction until symptoms' disappearance, with careful monitoring of patient's conditions and serum sodium concentration to avoid hyponatremia overcorrection. If the patient is symptomatic but hyponatremia occurred chronically, correction should be performed more gradually (1.5 to 2 mmol/L/h) [7].

Tolvaptan (TVP), an AVP receptor antagonist, represents a therapeutic option in these patients. It induces a net increase in free water excretion, decreasing aquaporin-2 channels in the renal collecting tubules and water re-absorption and consequently increasing serum sodium concentrations. This phenomenon causes a pure aquaresis without a rise of sodium or potassium urinary excretion [8].

Various studies have investigated the usefulness of TVP, revealing its safety and efficacy in hyponatremic patients, with additional benefits in terms of quality of life and reduced hospitalization [9, 10]. The correction of hyponatremia may also improve anti-neoplastic effects of chemotherapies [11], such as the decrease of AVP levels could reflect a neoplastic remission, or conversely, a recurrence [12].

Despite these findings, hyponatremia did not correlate with tumor burden. Although several studies have focused on hyponatremia in cancer patients, only a limited number of case reports of SIAD are available in this setting, and a limited amount of data on SIAD in cancer patients are available in the literature.

This observational, hypothesis generating study aimed to evaluate the efficacy and safety of TVP to treat and solve hyponatremia in oncologic patients with SIAD. Moreover, we compared TVP results with those obtained by intravenous (iv) therapy based on hypertonic solutions. The incidence of re-hospitalization, due to hyponatremia recurrence and consequent prognostic implication of TVP resistance was evaluated.

Patients and methods

15 adult patients, with a histologically confirmed diagnosis of solid pulmonary tumors who have developed SIAD between January 2017 and June 2020, were retrospectively enrolled in the study.
Diagnostic criteria confirmed the SIAD [13] by evaluating the volemic status, serum sodium concentration and serum osmolality, urine sodium concentration and urine osmolality, thyroid function tests, and serum cortisol. Hypovolemic and hypervolemic hyponatremia has been excluded, as well as hyponatremia due to other endocrine causes, including adrenal insufficiency or hypothyroidism.
Patients with transient hyponatremia due to drugs (i.e., antidepressants, anticonvulsants, antipsychotic), who did not feel thirsty or have difficulty drinking water, with urinary tract obstruction, with serum sodium levels <115 mEq/L associated with severe neurologic deficits, such as seizures, have been excluded from the study. Furthermore, heart failure, renal failure with a glomerular filtration rate < 60 ml/min, ascites associated with hepatic cirrhosis, nephrotic syndrome, severe arterial hypotension, evidence of urinary tract obstruction, poorly controlled diabetes mellitus, a recent history of myocardial infarction, and cerebrovascular disorders determined the exclusion from the enrolment.

Hyponatremia correction and follow-up

According to the pharmacological strategy, patients receiving TVP belonged to group A, whereas group B was characterized by hyponatremic patients treated with hypertonic saline solutions and fluid restriction. In particular, group A patients were treated with 7.5 mg/day of TVP on Day 1 and increased to 15 mg/day if no serum sodium increase was revealed. Conversely, an infusion of 1 ml/kg/h of 3% hypertonic saline was administered in group B, with serum sodium checked every 2 hours during the first 12 hours of treatment.

Patients were discharged and managed as outpatients if they met ambulatory criteria, once the maintenance dose of TVP had been determined. In particular, after the hospital discharge, all patients have been followed through a dedicated outpatient clinic system, with different timing according to clinical conditions and sodium levels. “Maintenance criteria” required weekly serum sodium evaluation before TVP administration, with a target of 2 mEq/L of sodium difference if compared with the concentration assessed at the hospital discharge or the last serum assessment. The liver function panel has been also monitored, as well as body weight and vital signs. Moreover, to avoid rapid and potentially dangerous sodium concentration increase, group A patients did not have a fluid restriction.

The current study was undertaken following the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all patients. Clinical data were collected from medical chart reviews and electronic records.

Statistical analysis

Statistical analyses were performed with NCSS for Windows (version 4.0), the MedCalc (version 11.0; MedCalc Software Acacialaan, Ostend, Belgium) software, and the GraphPad Prism (version 5.0; GraphPad Software, Inc., San Diego, CA, USA) package. Data were presented as mean ± SD for normally distributed values (at Kolmogorov-Smirnov test) and median [IQ range] for not normally distributed values. Differences between groups were established by unpaired t-test or by ANOVA followed by Bonferroni’s test for normally distributed values and by Kruskal-Wallis analysis followed by Dunn’s test for nonparametric values. Dichotomized values were compared using the χ^2 test. All results were considered significant if p was < 0.05.

Results

Patients baseline characteristics

	Total	Group A (TVP)	Group B (Hypertonic)	p
Patients	15	8	7	p > 0.05
Age, y	69.7±5.9	68.6±6.8	67.4±5.2	p > 0.05
WBC, mm^3	6.07±2.4	5.24±2.8	6.37±1.9	p > 0.05
eGFR	78.4±12.8	81.2±9.7	77.4±10.1	p > 0.05
Admission [Na], mmol/l	120.4±2.9	119.7±3.8	118.4±2.9	p > 0.05
Admission Serum Osmolality, mOsm/Kg	257±12.3	244.2±9.3	247±11.2	p > 0.05
Admission Urine Osmolality, mOsm/Kg	407±119.8	465±79.2	397±101	p > 0.05
Hospital stay, days	17.9±8.2	17.6±4.7	11.2±3.4	p < 0.01
Δ[Na], mmol/l/24h	7.9±4.4	8.7±3.5	7.4±4.2	p > 0.05
[Na] Target Achievement, days	6.4±3.6	3.7±2.8	5.2±3.1	p: 0.01
[Na] Hospital Discharge	143.8±1.8	143.4±2.6	144.2±2.1	p > 0.05
Hyponatremia recurrence				
Outpatients management, days	22.6±10.8	26.5±6.4	11±6.4	p < 0.01
Re-hospitalization, n (%)	8 (53)	3 (37)	5 (72)	p > 0.05
[Na] re-admission, mmol/l	122.7±2.8	123.9±3.4	121.4±3.7	p:0.03
Re-admission Serum Osmolality	251±9.4	262±7.9	258±4.5	p > 0.05
Re-admission urine Osmolality	504±104.8	472±93.4	408.5±79	p > 0.05
Disease progression, n (%)	5 (62)	3 (100)	2 (40)	p > 0.05

Table 1: Baseline characteristics of the study cohort.

A total of 15 patients (mean age: 69.7±5.9 years) were hospitalized because of SIAD, and the median sodium level at admission was 120.4±2.9 mmol/l (range 117.4-123.2 mmol/l). The median duration of hospitalization was 17.9±8.2 days (range 9.4-22.7 days). All patients underwent chest radiograph evaluation after the admission to the hospital, excluding active findings of pulmonary infection. The mean white blood cell count was 6.07±2.4 mm^3.

Hyponatremia management

Eight patients received tolvaptan for SIAD treatment (group A), whereas hypertonic solutions and fluid restriction have been the treatment for the remaining seven patients (group B).

In group A, all patients started tolvaptan at a dose of 7.5 mg/daily, with the next modifications according to sodium and osmolarity levels.

Hyponatremia has been improved in all Group A patients, without toxicity due to the drug, as revealed by normal values of liver function tests.

Serum sodium levels have been monitored over the first 24 h at regular intervals of 4-6 h to check the correction speed. A rapid correction was not observed, with a slow improvement of sodium levels within the range of 8-10 mmol/l/24h (ΔNa: 8.7±3.5 mmol/l/24h). Moreover, the correction of serum sodium, defined at 135 mmol/l, was achieved after 3.7±2.8 days. All patients required a final dose of 7 or 15 mg of TVP, before hospital discharge, as chronic therapy (Figure 1).

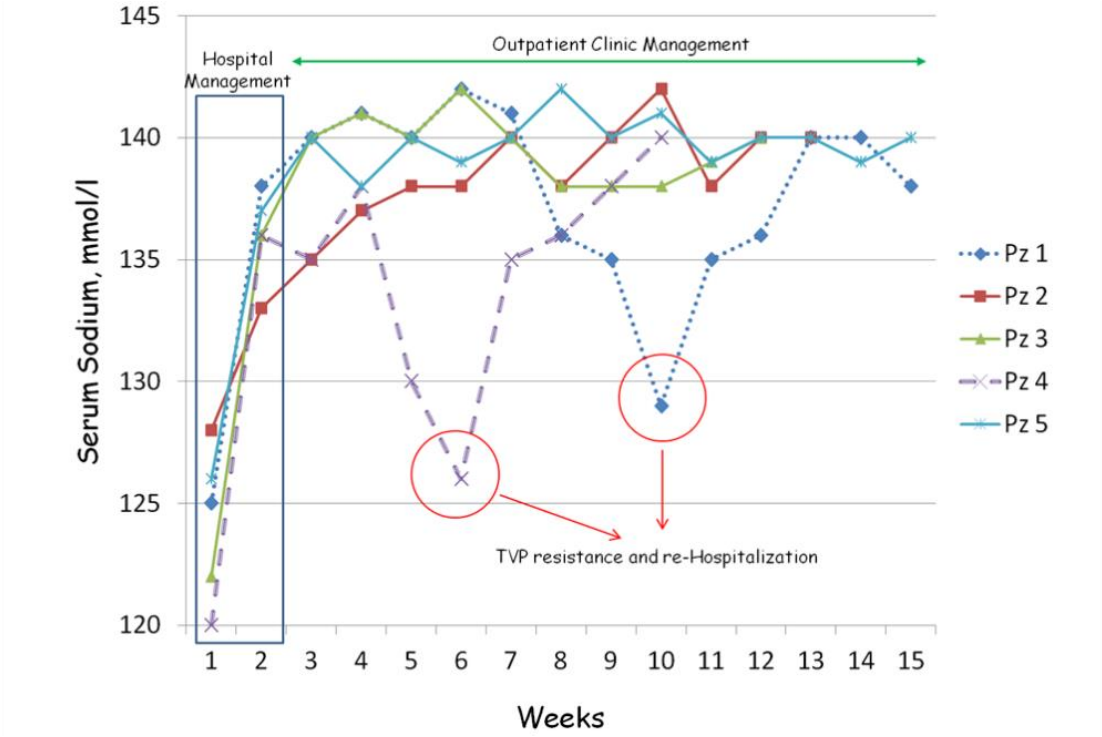

Figure 1: Sodium trend during tolvaptan administration.

In group B, patients had a similar trend for sodium increase (ΔNa: 7.4±4.2 mmol/l/24h), but the target levels were obtained more slowly, after 5.2±3.1 days (p: 0.01) than group A. Similarly, the hospital stay was longer in group B than in group A (17.6±4.7 vs 11.2±3.4 days; p< 0.01).

Hyponatremia relapse and re-hospitalization

Serum sodium levels were similar between the two groups during the last assessment in the hospital (143.4±2.6 vs 144.2±2.1; p> 0.05). After discharge, all patients have been followed weekly, to monitor clinical conditions and sodium levels.

Group B was characterized by a higher incidence of re-hospitalization than group A. In particular, 5/7 patients (72%) required hospitalization within 11±6.4 days after the discharge, due to symptomatic hyponatremia (mean serum sodium value at the hospital admission was 121.4±3.7 mmol/l), determining drowsiness, mental confusion or fatigue. This condition was solved by repeating intravenous schemes with hypertonic solutions, with a mean hospital stay of 13.6 ±7.2 days.

In TVP group A, only 3/8 patients (37%) had hyponatremic relapses. These three patients were managed in the outpatient clinic after 26.5±6.4 days (vs 11±6.4 days; p < 0.01) since the last hospital discharge. During this period, serum sodium was maintained between 140 and 145 mmol/l, administering 7.5 or 15 mg of TVP, daily or every other day. In these three patients, severe, sudden and detrimental hyponatremia was observed (123.9±3.4 mmol/l), requiring re-hospitalization. Notwithstanding the progressive increase of doses of TVP, from 7.5 or 15 mg to 60 mg per day hyponatremia did not improve, revealing a complete lack of response to TVP.

Behind planned protocols, the unscheduled oncologic and radiologic staging was early performed. In all three patients, a growth of tumor mass or new metastatic lesions has been revealed, requiring a re-scheduling and modification of chemotherapy cycles. Only after some chemotherapy administration, sodium levels slowly increased. Figure 2 synthetizes the events occurred in a patient with TVP resistance.

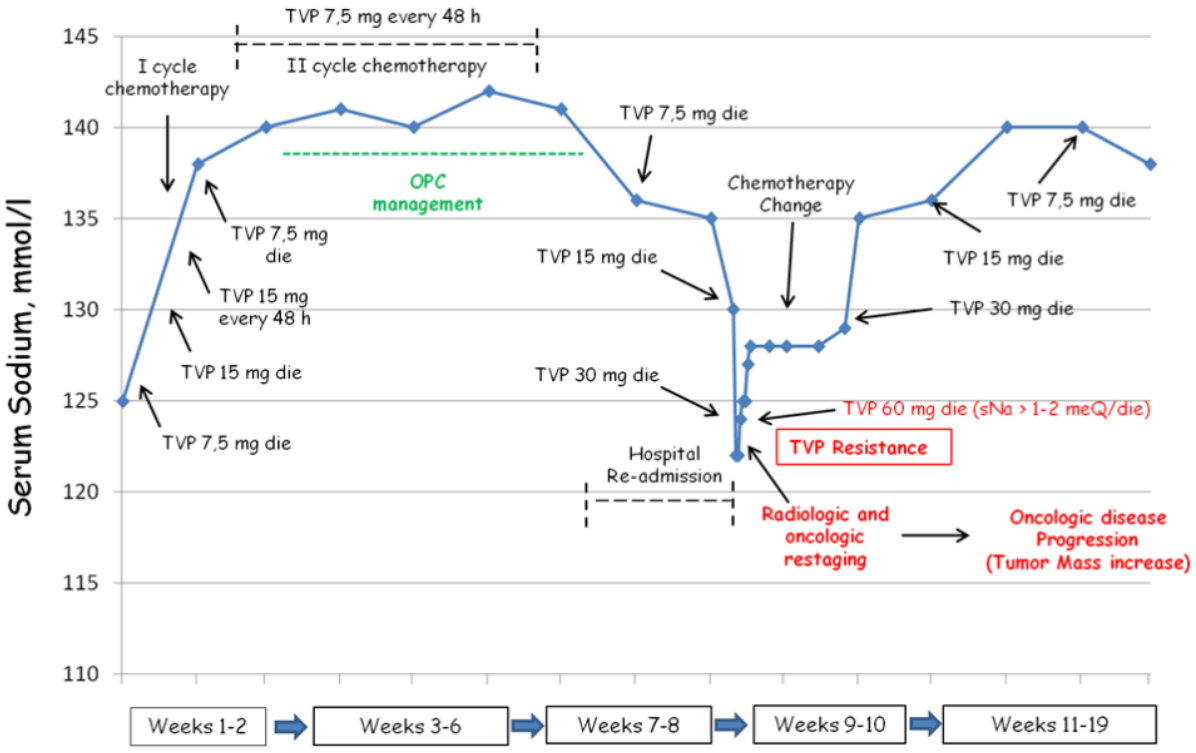

Figure 2: Management of hyponatremia and oncologic restaging in a patient with tolvaptan resistance.

In the remaining five patients (63%) of group A, hyponatremic episodes were often acutely and temporarily related to chemotherapy administration, with sodium correction after adjustment of TVP dose. These patients have been managed in outpatients clinic for more than six months, without the requirement of re-hospitalization and with no progression of cancer disease revealed after scheduled follow-up. All patients completed the planned chemotherapy.

No patients discontinued the TVP treatment due to adverse events, liver dysfunction, or serum sodium concentration exceeding 145 mEq/L.

Discussion

TVP represents a safe and valid therapeutic option to treat hyponatremic oncologic patients who developed SIAD, with no rapid sodium increase observed during the study period and without side effects TVP-related, such as sodium overcorrection or hepatic toxicity. Moreover, the aquaretic approach immediately increased serum sodium concentration, reducing the length of hospitalization, if compared to alternative methods, such as hypertonic solutions, reaching sodium normalization, but in fewer patients and in a longer time.

TVP also reduced the incidence of relapse of hyponatremia and re-hospitalization rate in outpatient follow-up, with obvious positive consequences on quality of life and costs.

These positive data also derived from specific clinical management of these patients, requiring multidisciplinary approaches and strategies, through a dedicated outpatient clinic system after the hospital discharge. Our patients have been evaluated with different timing, according to sodium levels and, consequently, TVP dosage adjustment.

A specific focus on these patients determined various supplementary effects, behind the issue “natremia”. During the follow-up, no TVP patients experienced acute kidney injury in concomitance with chemotherapeutical cycles, probably due to the diminished incidence of dehydration, secondary to fluid restriction, which could be usually prescribed in patients with low sodium levels.

The maintenance of serum sodium within the normal range allowed the precocious start of chemotherapeutic agents, without chemotherapy-related hyponatremia, due to the intravenous fluid overload and drug-associated AVP secretion. Behind these positive effects, related to the quick start of chemotherapy, TVP treatment facilitated the administration of chemotherapy cycles constantly and promptly, avoiding delays. Moreover, the efficacy of anticancer treatment is notably improved in patients with normal sodium levels or after its correction, as recently stated by Berardi who revealed an optimal sodium correction, an improvement of the hospitalization length and quality of life during TVP treatment [14].

Our study also suggested potential prognostic information that could be deduced from TVP patients, in whom sudden and progressive hyponatremia occurred, despite TVP dosage increase. A re-staging of these patients highlighted tumor mass growth or new metastatic lesions, suggesting cancer AVP production, requiring modification of chemotherapy cycles.

However, notwithstanding all this available evidence, the use of TVP remains limited in daily clinical practice, around 5%, according to the hyponatremia registry [15].

Adequate management of natremia is crucial due to the well-known correlation with overall survival, both in the general population and in cancer patients. Many studies revealed a close link between low sodium levels and poor prognosis, not only in small cell lung cancer [14] but also in other types of non-pulmonary tumors, including renal cell carcinoma and gastrointestinal cancer [16–19].

We cannot analyze potential relationships between survival and sodium correction, acutely or during a long follow-up period, by TVP administration due to the small cohort of patients.

The present study has some limitations that should be mentioned. First, the retrospective nature of this study could result in unwanted methodological biases. The therapy choices were not randomized; therefore, conclusions about the relative efficacy of the treatments, including TVP, are limited. Confirmation in wider cohorts is indispensable to attribute general validity to our results.

These limitations did not allow us to strengthen the prognostic role of TVP failure to improve sudden hyponatremia or to evaluate the impact of TVP therapy and sodium maintenance on patients' survival. However, our study generating hypotheses could be a starting point for further studies.

Conclusions

Our data demonstrated that TVP improved hyponatremia more efficiently and stably than hypertonic solutions and fluid restrictions, with a high rate of chemotherapeutical cycles concluded. Positive consequences have been obtained about the hospital stay, rate of relapse of hyponatremia, and re-hospitalization. TVP exerted its potential benefit of long-term use in an outpatient setting, improving the quality of life of SIAD oncologic patients.

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