Efficacy and safety of two different tolvaptan doses in the treatment of hyponatremia in the Emergency Department

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ABSTRACT

BACKGROUND: Hyponatremia (plasma sodium concentration or ${}_{P}[Na^{+}]$ < 136 mEq/L) is the most common electrolyte unbalance in clinical practice. Although it constitutes a negative prognostic factor, it frequently remains underdiagnosed and undertreated. Tolvaptan is an oral V_2-receptor antagonist which produces aquaresis. Given its emerging role in the treatment of dilutional hyponatremia, we aimed to compare the efficacy and safety of two different doses of this drug in an Emergency Department (ED) setting.

METHODS: Consecutive patients with moderate-to-severe euvolemic or hypervolemic hyponatremia were sequentially assigned to the 15 mg Group and to the 7.5 mg Group, and were revaluated at 6, 12 and 24 hours. Further evaluations and administrations were scheduled daily until ${}_{P}[Na^{+}]$ correction was achieved or the maximum period of 72 hours was exceeded. A one-month follow-up was performed.

RESULTS: Twenty-three patients were enrolled: 12 were included in the 15 mg Group, 11 in the 7.5 mg Group. Both doses significantly elevated the ${}_{P}[Na^{+}]$ over 24 hours, although the 15 mg Group showed faster corrections than the 7.5 mg Group (12 vs 6 mEq/L/24h; P = 0.025). An optimal correction rate (within 4-8 mEq/L/24h) was observed in 45.4% of the 7.5 mg Group against 25.0% (P n.s.). The standard dose led to dangerous overcorrections (> 12 mEq/L/24h) in 41.7% of the patients, while the low dose did not cause any (P = 0.037). No osmotic demyelination syndrome was observed.

CONCLUSIONS: A 7.5 mg tolvaptan dose can be considered both effective and safe in treating hyponatremia in the ED, while a 15 mg dose implicates too high a risk of overcorrection.

INTRODUCTION

Hyponatremia is defined as a plasma sodium concentration ($_P[Na^+]$) below 136 mEq/L; it can be classified as mild (130-135 mEq/L), moderate (125-129 mEq/L) and severe (< 125 mEq/L) [1]. Its prevalence amounts to 15-30% of hospitalized patients [2], 7% of whom are affected by moderate-to-severe forms [3]. Hyponatremia primarily affects the elderly [4,5] mostly as a chronic disorder, present in about 7-11% of outpatients [6].

Hyponatremia is often underestimated and undertreated: 17% of 3087 patients included in the Hyponatremia Registry received no treatment, and about 75% were discharged still hyponatremic [7].

When the $_P[Na^+]$ is particularly low, or the disease develops in less than 48 hours (acute hyponatremia), the osmotic gradient between brain cells and plasma induces cerebral edema. During chronic hyponatremia, brain cells compensate their transient hypertonicity preventing cerebral edema and maintaining the patient asymptomatic [8]. Hyponatremia represents an independent negative prognostic factor and predictor of mortality; it is still unclear whether hyponatremia reflects the severity of the underlying disorder, or plays an active role in increasing mortality [9], costs of hospitalization and readmission rates [10]. It is well-known that even mild chronic hyponatremia is associated with unapparent adverse events such as gait instability and attention deficit [11]; therefore treating hyponatremic patients is actually considered mandatory regardless of the absolute value of the $_P[Na^+]$.

Although hyponatremia often develops during hospitalization (the incidence being up to 15%) [12], it has been estimated that about 15-20% of the patients admitted to the Emergency Department (ED) are already hyponatremic [13].

The correct approach to hyponatremia needs to be addressed as to the identification of its pathophysiologic mechanism. According to the patient's volume status, hyponatremia is classified as hypovolemic, euvolemic and hypervolemic [1,14]. The precise correct diagnosis improves the clinical outcome [15,16], since hypovolemic hyponatremia is properly treated by infusing Na^+ in large volumes of fluid (i.e. normal saline, 0.9% NaCl), while the most targeted treatment of fluid overload hyponatremia is the elimination of the water excess (aquaresis) [17]. Aquaresis can be obtained using V_2-receptor antagonists, the vaptans, which block arginine-vasopressin (AVP)-dependent water reabsorption in the collecting ducts. AVP is deeply involved in the pathogenesis of hyponatremia due to fluid overload observed in chronic heart failure (CHF) or advanced hepatic cirrhosis, both characterized by an inappropriate AVP secretion [18,19].

Tolvaptan is an oral selective V_2-receptor antagonist approved in the US for the treatment of dilutional hyponatremia. The SALT trials demonstrate both efficacy and safety of a 15 mg starting dose [20]. Many studies demonstrate tolvaptan efficacy in long term treatments [21] and in many specific diseases such as: CHF [22-24], SIADH [25], or autosomal dominant polycystic kidney disease [26].

The FDA indicates tolvaptan as a therapeutic option for hospitalized symptomatic hyponatremic patients resistant to fluid restriction or for asymptomatic hyponatremic patients with a $_P[Na^+] < 125$ mEq/L [27]. Limited data are available on the use of tolvaptan in severe hyponatremia: few subjects enrolled in the SALT trials had a $_P[Na^+] < 125$ mEq/L, while a $_P[Na^+] < 120$ mEq/L in presence of neurological alterations constituted an exclusion criterion [20].

Infusions of hypertonic fluid boluses remain the gold standard treatment in patients with severe symptomatic hyponatremia (coma, dizziness, cardio-respiratory distress) [13].

No efficacy and safety data on tolvaptan in severe asymptomatic hyponatremia are available; on this basis, we wanted to investigate whether tolvaptan could be, in the ED, a valuable option as first therapeutic choice in hyponatremic patients, unless hypovolemic or presenting severe symptoms, regardless of the $_P[Na^+]$ at admission.

The latest review of the Literature set the optimal range of correction at 4-8 mEq/L/24h, and the safe upper limit at 12 mEq/L/24h [28]; in fact, previous studies show that a correction of about 4-6 mEq/L over 24 hours can usually remove all symptoms, [29] and a correction rate ≤ 12 mEq/L/24h is associated with a negligible risk of osmotic demyelination syndrome (ODS).

We aimed to identify the most appropriate starting dose selecting between the standard dose of 15 mg and a lower dose of 7.5 mg. This halved dose has been recently studied with encouraging results among selected subgroups of patients, [30,31] and has been suggested to be a safer option for the treatment of paraneoplastic SIADH [32].

METHODS

The study was designed as a non-randomized open-label trial, approved by the local Ethics Committee of the Maggiore della Carità University Hospital in Novara (CE 125/10, October 22nd, 2010). Consecutive patients affected by moderate-to-severe hyponatremia ($_{P}[Na^{+}]$ < 130 mEq/L) admitted to the ED from April 2012 to June 2015 were evaluated to assess their volume status by using a clinical algorithm based on recent medical history, physical examination and laboratory findings. Hypovolemia was determined by the presence of at least three of these criteria: vomiting, diarrhea, fever, hypotension, tachycardia, dry mucosae, dry axillary skin, positive pinch test, cold extremities, small pulse and thirst. Hypervolemia was assessed by the presence of at least two among peripheral edema, distended jugular veins, abdominojugular reflux, wet lung sounds, serous effusions and a $_{P}[Cl^{-}]/_{P}[Na^{+}]$ between 0.716-0.784 [33]. Normovolemic and hypervolemic patients were considered eligible for this trial.

Exclusion criteria were age < 18 years, acute hyponatremia (i.e., hyponatremia for less than 48 hours), clinical hypovolemia, presence of severe symptoms (seizures, deep drowsiness or a Glasgow Coma Score < 9), acute coronary syndrome, respiratory distress, major trauma, stroke, shock, hyperglycemia (blood glucose > 250 mg/dL), chronic kidney disease (eGFR < 30 mL/min), or lack of informed consent.

The study was carried out in the ED Observation Unit of the Novara University Hospital. The maximum study period was set at 72 hours.

Each patient received the first tolvaptan dose, and was evaluated after 6, 12 and 24 hours by collecting data helpful in establishing water and Na^{+} balance (such as urine output, weight, plasma and urine electrolytes concentration). In order to keep a negative water balance, patients underwent a controlled regimen of fluid intake. Drugs potentially responsible for hyponatremia were withdrawn.

When required, further evaluations and further tolvaptan administrations were scheduled every 24 hours until a $_{P}[Na^{+}]$ value ≥ 130 mEq/L was obtained, or the time limit of 72 hours was reached.

Patients were consecutively assigned to two different tolvaptan daily doses (15 or 7.5 mg). Since tolvaptan (Samsca®) is only available in 15 and 30 mg tablets, the Pharmaceutical Service of the Maggiore della Carità Hospital cut 15 mg tablets in half in order to obtain the low tolvaptan dose.

When the $_{P}[Na^{+}]$ correction was obtained, asymptomatic patients attended an educational program and were discharged. A telephonic follow-up was scheduled 1 month later.

If the $_{P}[Na^{+}]$ did not improve and the clinical conditions of the patients tended to deteriorate, an infusion of 2 mL/kg of hypertonic saline solution (3% NaCl) was performed as a rescue treatment. Patients with less severe symptoms but still hyponatremic or presenting other clinical problems at the end of the study, were admitted to the appropriate hospital ward (usually Internal Medicine).

Patients presenting overcorrection withdrew tolvaptan therapy, were encouraged to increase water intake, and were clinically observed in order to exclude neurological impairment during the next hours.

In order to establish efficacy and safety of the two tolvaptan doses, we used the increase in $_{P}[Na^{+}]$ ($\Delta_{P}[Na^{+}]$) over 24 hours to define four different correction categories [28]:

- ✓ low degree of correction: < 4 mEq/L/24h;
- ✓ optimal correction: 4-8 mEq/L/24h;
- ✓ mild (or low risk) overcorrection: 9-12 mEq/L/24h;
- ✓ severe (or high risk) overcorrection: > 12 mEq/L/24h.

The primary efficacy endpoints were to evaluate the ability of a low tolvaptan dose to obtain a statistically significant increase in the $_{P}[Na^{+}]$ with respect to baseline values, and to compare the efficacy of the two tolvaptan doses. Secondary endpoints related both to efficacy and safety. The correction kinetics were used to evaluate the percentage of patients who experienced correction rates within the optimal range [28]. Subjects were also divided into two subgroups according to their

baseline $_P[Na^+]$ by setting a cut-off at 120 mEq/L. Correction rates between subgroups were then compared.
Clinically relevant adverse events were recorded, and the correction kinetics was used to determine the occurrence of overly rapid correction.
Before discharge, patients were given an educational program about diet, fluid intake and correct use of diuretics in order to prevent the relapse of hyponatremia.
Each patient was asked to check his $_P[Na^+]$ 30 days after tolvaptan withdrawal, and was then contacted by telephone for a structured interview to detect symptoms or adverse events.
Statistical analysis were performed using the MedCalc® software v12.5.0 (MedCalc software bvba – Ostend, Belgium). Continuous data were analyzed through the Mann-Whitney U test, while the two-tailed Fisher's exact text was used to analyze categorical data. Statistical significance was set at $P < 0.05$.

RESULTS

We enrolled 23 hyponatremic patients from April 2012 to June 2015. The median age was 76 (63 to 91), 17 subjects were women (73.9%), 18 (78.3%) received diuretic treatment, 20 (87.0%) took at least 4 drugs daily and 12 (52.2%) were affected by at least 3 active chronic diseases. At ED admission, 11 patients (47.8%) showed signs or symptoms attributable to hyponatremia as summarized in ***Table 1***; the remaining 12 were *asymptomatic* on ED evaluation, and their hyponatremia was occasionally found while dealing with different clinical pictures (mostly acute heart failure). Moreover 7 subjects (30.4%) had a baseline $_P[Na^+] < 120$ mEq/L.
The first 12 patients recruited received a standard tolvaptan dose (15 mg Group), while the next 11 were treated with a low dose (7.5 mg Group). The two groups had comparable median $_P[Na^+]$ (125 mEq/L vs 124 mEq/L) and comparable median ages (77 years vs 76 years, *P*-value n.s. for both). In the 15 mg Group, 66.7% of the patients were females, 83.3% were under diuretic therapy and 91.7% took at least 4 different drugs daily, against 81.8%, 72.7% and 81.8%, respectively, of the other group. ***Tables 2*** and ***3*** show the comparisons of baseline data between groups.
Only 1 patient in the 15 mg Group (8.2%) required a second tolvaptan administration, while 7 patients (63.6%) in the 7.5 mg Group (63.6%) took at least two doses; 2 patients (18.2%) in the low dose group took tolvaptan for three consecutive days and 1 of them failed to achieve a $_P[Na^+]$ correction within 72 hours. This latter patient, as well as another one, required hospitalization; all the remaining 9 patients were discharged. In the 15 mg Group, 3 patients (25.0%) were hospitalized, although $_P[Na^+]$ correction had been already obtained, because of heart failure, pneumonia and multiple myeloma. ***Table 4*** shows the total cumulative tolvaptan dose and the cumulative duration of therapy in the ED for the two groups.
Given the high number of patients who successfully corrected their $_P[Na^+]$ within the first 24 hours in the 15 mg Group, we focused our analysis on the first 24 hours.
Twenty-four hours after tolvaptan administration, the median $_P[Na^+]$ was 132 mEq/L in the 15 mg Group (min 126 mEq/L, max 139 mEq/L) and 130 mEq/L in the 7.5 mg (min 111 mEq/L, max 135 mEq/L). A statistically significant difference was observed between median $_P[Na^+]$ at baseline and after 24 hours in both 15 and 7.5 mg Groups ($P = 0.0004$ and $P = 0.011$ respectively).
The difference between the serial $_P[Na^+]$ measurements with respect to the baseline $_P[Na^+]$ was defined as $\Delta_P[Na^+]$ and was used to describe the correction kinetics after tolvaptan administration (***Fig. 1***):

- ✓ at 6 hours the $\Delta_P[Na^+]$ was 3 mEq/L (min 1 mEq/L, max 12 mEq/L) in the 15 Group and 2 mEq/L (min -1 mEq/L, max 7 mEq/L) in the 7.5 mg Group ($P = 0.158$);
- ✓ at 12 hours the $\Delta_P[Na^+]$ was 9 mEq/L (min 3 mEq/l, max 21 mEq/L) in the 15 mg Group and 4 mEq/L (min 1 mEq/L, max 12 mEq/L) in the 7.5 mg Group ($P = 0.042$);
- ✓ at 24 hours the $\Delta_P[Na^+]$ was 12 mEq/L (min 6 mEq/L, max 25 mEq/L) in the 15 mg Group and 6 mEq/L (min 1 mEq/L, max 11 mEq/L) in the 7.5 Group ($P = 0.025$).

The faster correction rates observed in the 15 mg Group were accompanied by a larger urine output over the 24 hour-period (***Fig. 2a-2b***): the median daily urine output was 4000 mL (min 1550 mL, max 9750 mL) in this group, compared to 2000 mL (min 1100 mL, max 3100 mL) in the 7.5 mg Group (P = 0.014).

In the 15 mg Group, the comparison of the 24-hour $\Delta_P[Na^+]$ between patients with a baseline $_P[Na^+]$ < 120 mEq/L and patients with a baseline $_P[Na^+]$ ≥ 120 mEq/L showed a clear difference (20 mEq/L/24h vs 8 mEq/L/24h) that, however, did not reach full statistical significance (P = 0.053). The same trend was observed in the 7.5 mg Group, but the difference was smaller (8 mEq/L/24h vs 4 mEq/L/24h; P = 0.156) (***Fig. 3***).

Considering the median values of the $\Delta_P[Na^+]$ obtained 24 hours after tolvaptan administration, the 7.5 mg Group shows a median correction rate of 6 mEq/L/24 h, perfectly included within the optimal range (4-8 mEq/L/24h), while the 15 mg Group has a higher median correction rate (12 mEq/L/24h).

In the 15 mg Group only 25.0% of patients showed optimal correction rates, compared to 45.4% in the 7.5 Group (P = 0.400). None of the patients in the standard dose group experienced a low degree of correction ($\Delta_P[Na^+]$ < 4 mEq/L/24h), against 27.3% of the low dose group. Correction rates > 8 mEq/L/24h were observed in 75.0% of the patients in the 15 mg Group and in 27.3% in the 7.5 mg Group.

By splitting again this latter category, it is possible to separate those patients who did not achieve an optimal correction rate ($\Delta_P[Na^+]$ within 9 and 12 mEq/L/24h) from those who actually experienced an overcorrection ($\Delta_P[Na^+]$ > 12 mEq/L/24h), thus commuting the efficacy analysis into a safety analysis. None of the patients in the 7.5 mg Group exceeded 12 mEq/L/24h, against 41.7% in the 15 mg Group (P = 0.037) (***Fig. 4***).

The 1-month follow-up results are available for 19 patients (82.6%): 1 patient in the 7.5 mg Group and 3 patients in the 15 mg Group were lost to follow-up. All patients of the low dose group were still alive 30 days after the end of the study and their median $_P[Na^+]$ was 137 mEq/L. Three patients treated with 15 mg died during the follow-up period, but their deaths were related neither to hyponatremia nor to tolvaptan treatment (1 patient died because of respiratory failure and 2 because of heart failure). The 6 remaining patients of this group were available for the follow-up interview and showed a median $_P[Na^+]$ of 136 mEq/L at 30 days. The statistical analysis of the 1-month mortality did not show a significant difference between the two groups.

DISCUSSION

Hyponatremia is the most frequent electrolyte disorder observed in clinical practice. Its prevalence in ED patients is probably 15-20% [13]. Even though it is associated with poor outcome and prolonged hospitalization [9] hyponatremia is currently underdiagnosed and undertreated in the ED worldwide. In the last 10 years many studies have demonstrated efficacy and safety of vaptans in treating patients with hypervolemic and normovolemic hyponatremia [20,34-37]; none of them was carried out in the ED. Actually, two different meta-analysis involving a large number of clinical trials on different vaptans show little effect of these drugs in increasing the $_P[Na^+]$ and no effect on mortality [38,39].

With this pilot study we intended to investigate efficacy and safety of two tolvaptan doses in treating hyponatremic patients in the ED.

Out of the 23 hyponatremic patients we enrolled, 12 received the standard tolvaptan daily dose of 15 mg while 11 received an halved dose.

Our results confirm the efficacy of the standard tolvaptan dose and, as expected on the basis of the report of the Hyponatremia Registry and of other retrospective studies [7,40], the median $_P[Na^+]$ increase we found was substantially higher compared to those described in the SALT trials [20]. All patients treated with the standard tolvaptan dose showed an increase in the $_P[Na^+]$ of at least 6 mEq/L in the first 24 hours, with a median increase in the $_P[Na^+]$ of 12 mEq/L. Although the correction rates observed in this group exceeded the values recommended by recent guidelines in 75.0% of patients [13,28], we observed no ODS; this is in line with the results of many trials and retrospective investigations in which vaptans-related ODS were not observed [13]. Nevertheless,, experimental animal models of chronic hyponatremia have demonstrated that these drugs can induce the same changes in osmotic gradients and encephalic damages (including ODS) produced by improper infusive therapies [41]. This remarks the importance of a careful use of vaptans in this setting since the risk of ODS actually exists, and the lack of vaptans-related ODS might be explained by the recent awareness of safer correction rates, and by the knowledge that the $_{P}[Na^{+}]$ should be promptly re-lowered in patients experiencing overly rapid corrections.

Tolvaptan ability in increasing the $_{P}[Na^{+}]$ is also confirmed with the 7.5 mg dose, but the correction rate is lower compared to the standard dose; though apparently predictable, this observation is partially in conflict with a very recent retrospective study that reports similar mean daily correction rates with the two doses (9.8 ± 2.9 mEq/L vs 9.9 ± 3.9 mEq/L) [41]. This study was focused on consecutive patients affected by SIADH and treated with tolvaptan; however, all the 6 patients treated with 7.5 mg presented with severe hyponatremia, and this characteristic could fully explain their higher correction rates.

In our study, about 90% of the patients treated with 7.5 mg show an increase in the $_{P}[Na^{+}]$ of at least 3 mEq/L/24h, while the median rise in the $_{P}[Na^{+}]$ observed in the first 24 hours is 6 mEq/L (min 1 mEq/L, max 11 mEq/L), and the percentage of patients who obtain an optimal correction rate (4-8 mEq/L) is 45.4%.

Only 1 patient failed to achieve a $_{P}[Na^{+}]$ of at least 130 mEq/L during the 72-hour period. It should not be considered a treatment failure because the starting $_{P}[Na^{+}]$ was 102 mEq/L and after 72 hours the $_{P}[Na^{+}]$ was 114 mEq/L; in the case of such a severe chronic hyponatremia, a mean daily rise in the $_{P}[Na^{+}]$ of 4 mEq/L/24h is both adequate and safe, and is consistent with Literature's recommendations [28].

Interestingly, we observed differences in the correction kinetics depending on the baseline $_{P}[Na^{+}]$. Patients with lower starting $_{P}[Na^{+}]$ had the tendency to experience faster correction rates than patients with higher starting $_{P}[Na^{+}]$. Our observations are completely in line with an assumption already described both for traditional and for tolvaptan treatments: the lower the $_{P}[Na^{+}]$ is at baseline. the higher tends to be the correction rate [20,29,40].

We observed a significant reduction in the occurrence of overcorrections in patients treated with 7.5 mg compared to the standard dose both with the conventional cut-off of 12 mEq/L/24h (0.0% vs 41.7%) and with the more restrictive one of 8 mEq/L/24h (27.3% vs 75.0%). Although no severe adverse event was observed in our patients, we believe that, in the ED, a starting tolvaptan dose of 7.5 mg is safer considering that patients are heterogeneous and often affected by multiple comorbidities and under multi-drug therapies; moreover, much important information, such as the time of onset of hyponatremia and the normal body weight, are often unavailable or unreliable. Additionally, the superiority of the halved dose in terms of safety is even clearer in patients with severe hyponatremia, who are those at the highest risk to develop ODS after overly rapid corrections.

As shown in ***Table 4***, the duration of treatment in 15 mg Group is significantly shorter compared to 7.5 mg Group; this difference could be misleading since it reflects the high incidence of overcorrection observed in 15 mg Group, and demonstrates the safer correction kinetics obtained with the low dose.

The main limitation of this work is the lack of randomization and the unblinded design. Moreover, the criteria used to select eligible patients were essentially clinical, and no instrumental analysis was carried out to confirm the patients' volume status. However, the study aimed to evaluate the potential role of tolvaptan in the treatment of hyponatremia in the ED, where the first evaluation of patients necessarily relies on essential clinical parameters and on a few readily and widely available laboratory tests.

In conclusion, the data presented in this study demonstrate that a 7.5 mg tolvaptan dose can be considered an effective and safe alternative to infusive therapy as first approach to euvolemic and hypervolemic hyponatremia in an ED setting. On the other hand, our results raise concerns about safety of the 15 mg tolvaptan dose as first therapeutic approach in patients presenting hyponatremia, as it implicates an high risk of overly rapid correction. The main future developments of our findings would concern the possibility to discharge low risk patients with the prescription of a home low dose tolvaptan therapy and a close revaluation. This therapeutic strategy needs to be associated with a correct information about water intake and a careful revision of home therapy. In our opinion it could eventually reduce hospitalizations and, hopefully, costs, as it would allow us to treat in a simple way a large number of cases of a widespread and insidious disease that, according to the Literature, still remains frequently untreated.

TABLES

Signs and symptoms of hyponatremia	7.5 mg			15 mg			*P-value*
	Yes (%)	**No (%)**	**Missing data (%)**	**Yes (%)**	**No (%)**	**Missing data (%)**	
Confusion or drowsiness	18.2	81.8	0	8.3	91.7	0	0.590
Disorientation in time, place or person	9.1	90.9	0	8.3	91.7	0	1.000
Cognitive-motor slowing	36.4	63.6	0	8.3	91.7	0	0.155
Subjective dizziness	36.4	54.5	9.1	8.3	91.7	0	0.135
Gait instability ± falls	27.3	63.6	9.1	16.7	83.3	0	0.624
Abdominal pain	18.2	72.7	9.1	0	100	0	0.195
Nausea ± vomiting	18.2	72.7	9.1	16.7	83.3	0	1.000
Headache	9.1	81.8	9.1	8.3	91.7	0	1.000
Fatigue or general malaise	18.2	72.7	9.1	8.3	91.7	0	0.571

Table 1 Percentage frequencies of signs and symptoms potentially related to the hypotonic state induced by hyponatremia. No statistically significant difference emerged in the frequency of these findings between the two groups.

Continuous variable	7.5 mg	15 mg	*P-value*
Age (years)	76 [IQR 65 – 83]	77 [IQR 73 – 82]	0.424
Systolic arterial blood pressure (mmHg)	130 [IQR 119 – 160]	138 [128 – 149]	0.877
Diastolic arterial blood pressure (mmHg)	75 [IQR 61 – 88]	78 [IQR 68 – 85]	1.000
Mean arterial blood pressure (mmHg)	90.00 [IQR 82.73 – 116.67]	97.50 [IQR 90.84 – 101.67]	0.782
Heart rate (bpm)	66 [IQR 61 – 78]	86 [IQR 72 – 93]	0.009
Body temperature (°C)	36.0 [IQR 35.7 – 36.4]	36.0 [IQR 36.0 – 36.6]	0.261
Weight (kg)	59.0 [IQR 42.0 – 69.0]	63.8 [IQR 38.8 – 82.5]	0.248
BMI (kg/m^2)	24.32 [IQR 17.98 – 29.31]	25.38 [IQR 22.44 – 29.77]	0.413
Blood glucose (mg/dL)	120 [IQR 100 – 143]	151 [IQR 96 – 227]	0.491
$_{P}[Cr]$ (mg/dL)	0.76 [IQR 0.60 – 0.85]	0.88 [IQR 0.78 – 1.01]	0.207
$_{P}[Na^+]$ (mEq/L)	124 [IQR 119 – 128]	125 [IQR 118 – 127]	0.951
$_{P}[Cl^-]$ (mEq/L)	92 [IQR 86 – 97]	91 [IQR 86 – 94]	0.355
$_{P}[K^+]$ (mEq/L)	4.5 [IQR 4.1 – 5.1]	4.2 [IQR 3.7 – 4.5]	0.196
$_{U}[Cr]$ (mg/dL)	51.6 [IQR 31.0 – 92.0]	38.4 [IQR 17.6 – 73.7]	0.320
$_{U}[Na^+]$ (mEq/L)	55 [IQR 35 – 88]	66 [IQR 32 – 81]	0.887
$_{U}[Cl^-]$ (mEq/L)	72 [IQR 36 – 99]	64 [IQR 37 – 88]	1.000
$_{U}[K^+]$ (mEq/L)	29.3 [IQR 21.4 – 66.6]	24.6 [IQR 15.0 – 38.1]	0.286
$FENa^+$ %	0.42 [IQR 0.25 – 1.05]	1.25 [IQR 0.31 – 2.21]	0.166
$_{P}[Cl^-]/_{P}[Na^+]$	0.76 [IQR 0.73 – 0.76]	0.74 [IQR 0.71 – 0.76]	0.306

Table 2 Medians and interquartile range of the main continuous variables evaluated before tolvaptan administration in the two treatment groups. Apart from the isolated exception of heart rate, statistically significant differences were not observed in the medians of these parameters between the two groups. BMI = body mass index; $_{P}[Cr]$ = plasma creatinine concentration; $_{P}[Na^+]$ = plasma sodium concentration; $_{P}[Cl^-]$ = plasma chloride concentration; $_{P}[K^+]$ = plasma potassium concentration; $_{U}[Cr]$ = urine creatinine concentration; $_{U}[Na^+]$ = urine sodium concentration; $_{U}[Cl^-]$ = urine chloride concentration; $_{U}[K^+]$ = urine potassium concentration; $FENa^+$ = fractional Na^+ excretion.

Categorical variable	7.5 mg			15 mg			*P-value*
	Yes (%)	No (%)	Missing data (%)	Yes (%)	No (%)	Missing data (%)	
Protracted vomiting (> 3 episodes/h) or protracted diarrhea (> 10 episodes/die)	0	100	0	8.3	91.7	0	1.000
External body temperature > 38 °C in the previous 48 h	0	100	0	16.7	83.3	0	0.478
Bedridden	18.2	81.8	0	16.7	83.3	0	1.000
Thirst	36.4	63.6	0	41.7	58.3	0	1.000
Hypotension (SABP) < 100 mmHg)	0	100	0	0	100	0	1.000
Orthostatic hypotension	0	81.8	18.2	0	75.0	25.0	0.471
Tachycardia (HR > 100 bpm) and/or raise in the HR in orthostatism > 30 bpm	0	100	0	8.3	91.7	0	1.000
Dry mucosae	18.2	81.8	0	50.0	50.0	0	0.193
Positive pinch test	0	100	0	25.0	75.0		0.217
Dry axillary skin	0	100	0	0	100	0	1.000
Small pulse	9.1	90.9	0	8.3	91.7	0	1.000
Cold extremities	9.1	90.9	0	25.0	75.0	0	0.590
Distended neck veins	9.1	90.9	0	50.0	50.0	0	0.069
Abdominojugular reflux	9.1	90.9	0	8.3	91.7	0	1.000
Peripheral edema	27.3	72.7	0	66.7	33.3	0	0.100
Wet lung sounds	9.1	90.9	0	16.7	83.3	0	1.000
Pleural effusion	9.1	90.9	0	16.7	83.3	0	1.000
Ascites	0	100	0	8.3	91.7	0	1.000
$0.715 < {}_{P}[Cl^-]/{}_{P}[Na^+] < 0.785$	81.8	9.1	9.1	58.3	41.7	0	0.162

Table 3 Percentage frequencies of the main categorical variables investigated at the moment of the volume assessment. Elements strongly consistent with dehydration or hypovolemia (hypotension or orthostatic hypotension) were found in none of the patients in the two groups. Some of them showed physical evidences of water excess (peripheral edema, distended neck veins). Apart from the isolated exception of distended neck veins, no statistically significant difference was observed in the distribution of the findings given in this table between the two groups. h = hours; SABP = systolic arterial blood pressure; HR = heart rate; ${}_{P}[Na^+]$ = plasma sodium concentration; ${}_{P}[Cl^-]$ = plasma chloride concentration.

Group	7.5 mg	15 mg
Tolvaptan cumulative dose (mg)	13.64	16.25
Cumulative duration of therapy (h)	43.64	26.00

Table 4. Tolvaptan cumulative dose administered during the study period and cumulative duration of therapy in the ED in the two groups.

FIGURE CAPTIONS:

Fig. 1 The graph compares the increase in $_P[Na^+]$ at each revaluation time (6, 12 and 24 hours) from baseline values between patients treated with the standard dose (light bars) and patients treated with the low dose (dark bars). The difference between the two groups reached statistic significance 12 hours after tolvaptan administration and was still significant at the end of the 24-hour period. $\Delta_P[Na^+]$ = difference between the $_P[Na^+]$ measured at each revaluation and the $_P[Na^+]$ measured at baseline.

Fig. 2a The graph represents the time courses of the $_P[Na^+]$ in the two groups during the first 24 hours of treatment. Despite a similar rapid rise until 6 hours after tolvaptan administration, the patients treated with 15 mg kept an higher correction rate throughout the remaining 18 hours of therapy thus reaching an higher final $_P[Na^+]$ than those who received the low dose (7.5 mg).

Fig. 2b The graph represents the time course of urine output in the two groups during the first 24 hours of treatment. The larger diuresis observed in the 15 mg Groups reflects the higher correction rate described in *Fig. 2a* and is substantially consistent with the dose-dependent aquaretic effect of tolvaptan.

Fig. 3 Patients with lower $_P[Na^+]$ at baseline exhibit higher correction rates than those starting from less hyponatremic values. The difference between the two subgroups was near borderline significance in the 15 mg Group. In the 7.5 mg Group this trend is substantially confirmed, but the difference is smaller and *P-value* is further from statistical significance.

Fig. 4 In the 7.5 mg Group 45.4% of the patients have a correction rate within the optimal range of 4 to 8 mEq/L/24h while in the 15 mg Group only 25.0% of the patients meet this criterion of effectiveness. A low degree of correction is observed in 27.3% of the patients treated with the low dose, while none of the patients who received the standard dose have a correction rate < 4 mEq/L/24h. In the 7.5 mg Group, 27.3% of the patients showed correction rates exceeding the upper limit of the optimal range (low risk overcorrection), compared to 33.3% of the other group. No high risk overcorrection was observed in patients treated with the low dose, while in the 15 mg Group 41.7% experienced correction rates > 12 mEq/L/24h. However, none of them developed an ODS.

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