Equivalent Efficacy and Decreased Rate of Overcorrection in Patients With Syndrome of Inappropriate Secretion of Antidiuretic Hormone Given Very Low-Dose Tolvaptan

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Rationale & Objective: Euvolemic hyponatremia often occurs due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Vasopressin 2 receptor antagonists may be used to treat SIADH. Several of the major trials used 15 mg of tolvaptan as the lowest effective dose in euvolemic and hypervolemic hyponatremia. However, a recent observational study suggested an elevated risk for serum sodium level overcorrection with 15 mg of tolvaptan in patients with SIADH.

Study Design: A retrospective chart review study comparing outcomes in patients with SIADH treated with 15 versus 7.5 mg of tolvaptan.

Settings & Participants: Patients with SIADH who were treated with a very low dose of tolvaptan (7.5 mg) at a single center compared with patients using a 15-mg dose from patient-level data from the observational study described previously.

Predictors: Tolvaptan dose of 7.5 versus 15 mg daily.

Outcomes: Appropriate response to tolvaptan, defined as an initial increase in serum sodium level > 3 mEq/L, and overcorrection of serum sodium level (>8 mEq/L per day, and >10 mEq/L per day in sensitivity analyses).

Analytical Approach: Descriptive study with additional outcomes compared using *t* tests and F-tests (Fischer's Exact χ2 Test).

Results: Among 18 patients receiving 7.5 mg of tolvaptan, the mean rate of correction was 5.6 ± 3.1 mEq/L per day and 2 (11.1%) patients corrected their serum sodium levels by >8 mEq/L per day, with 1 of these increasing by >12 mEq/L per day. Of those receiving tolvaptan 7.5 mg, 14 had efficacy, with increases ≥ 3 mEq/L; similar results were seen with the 15-mg dose (21 of 28). There was a statistically significant higher chance of overcorrection with the use of 15 versus 7.5 mg of tolvaptan (11 of 28 vs 2 of 18; $P = 0.05$; and 10 of 28 vs 1 of 18; $P = 0.03$, for >8 mEq/L per day and >10 mEq/L per day, respectively).

Limitations: Small sample size, retrospective, and nonrandomized.

Conclusions: Tolvaptan, 7.5 mg, daily corrects hyponatremia with similar efficacy and less risk for overcorrection in patients with SIADH versus 15 mg of tolvaptan.

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Hyponatremia is the most common electrolyte disorder in hospitalized patients.[1] Hyponatremia can be caused by fundamentally different physiologic mechanisms that include a discrepancy in water input and output (true hypo-osmolar hyponatremia), transcellular water shifts (true hyperosmolar hyponatremia secondary to hyperglycemia), or changes in the fraction of plasma occupied by water (pseudohyponatremia due to hyperlipidemia and hyperproteinemia).[2] In addition to this categorization, hyponatremia is subcategorized by the volume status of patients; that is, hypovolemic, euvolemic, or hypervolemic.[3] The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is the most common cause of euvolemic hyponatremia.[4]

SIADH may be triggered by a variety of conditions, including medications, malignancy, pain, nausea and vomiting, infections, or neurologic/central causes.[5] The common finding of patients with SIADH is the increased level of antidiuretic hormone relative to their physiologic needs.[5] Patients with SIADH have increased urinary fractional excretion of sodium (Na^+), urea, and uric acid[6-8]; elevated urine osmolality[6]; and worsening of hyponatremia with isotonic fluid infusion[9] in patients with urinary sodium plus potassium concentration ($[Na^+ + K^+]$) > 154 mmol/L.[10]

Before the development of vasopressin 2 (V2) receptor antagonists (vaptans), treatment of SIADH focused on water restriction, sodium tablets with diuretics, and 3% normal saline solution in cases of severe symptomatic hyponatremia,[5] demeclocycline, and urea intake.[1] The development of medications such as tolvaptan gave physicians the ability to target the end effect of antidiuretic hormone.[11] However, these agents were associated with significant risks, including abnormal liver function test results and the possibility of hyponatremia overcorrection, potentially resulting in osmotic demyelination syndrome[12-16] (Fig S1). Urea, although safer, is poorly palatable.

The risk for hyponatremia overcorrection has been difficult to predict mathematically with existing sodium modeling equations and commonly available inpatient measurements, particularly in dynamic conditions and

overextended periods of time.[17-19] Instances of overcorrection were reported particularly in elderly female malnourished patients and patients who had SIADH,[12,20] increasing their risk for osmotic demyelination syndrome.[15,21] In 2017, Kamgar et al[22] suggested evidence of the risk for hyponatremia overcorrection in patients with SIADH on the lowest recommended dose of tolvaptan (15 mg). Accordingly, the authors recommended the use of tolvaptan, 7.5 mg, in patients with SIADH to avoid overcorrection.[22] These findings are in contrast to data in the Study of Ascending Levels of Tolvaptan in Hyponatremia 1 (SALT-1), SALT-2, and SALT-3 trials, which included mostly hypervolemic patients receiving 15 mg of tolvaptan who had a low probability of overcorrection.[23-25]

Morris et al[20] showed that patients with SIADH who received tolvaptan responded differently than volume-overloaded patients with congestive heart failure and hyponatremia. Specifically, 28.6% (8/28) of patients with SIADH receiving 15 mg of tolvaptan had their serum [Na^+] increased by >12 mEq/L within a 24-hour period, exceeding the recommended guidelines of 8 to 10 mEq/L per day or less.[20] In 39.3% (11/28) of patients, serum [Na^+] corrected at a rate > 8 mEq/L within a 24-hour period.[26-28] There were 6 patients reported in supplementary data in that study who received 7.5 mg of tolvaptan, but no statistical analysis of their response was attempted.[20] Importantly, this dose is lower than the US Food and Drug Administration's minimum recommended dose.[23]

Therefore, in the present study, we performed a retrospective analysis of patients with SIADH receiving low-dose tolvaptan (7.5 mg) in comparison to standard therapy (tolvaptan, 15 mg) to determine the dose-dependent efficacy of correction and risk for overcorrection of serum [Na^+] in patients with SIADH.

METHODS

A retrospective study was performed to investigate the change in serum [Na^+] in patients with SIADH after administration of 7.5 mg of tolvaptan. The project was approved under University of California, Los Angeles (UCLA) Institutional Review Board #17-001783. This work adheres to the Declaration of Helsinki regarding human subject research.

Patient Selection

The UCLA electronic medical record system (EPIC) was queried for the following parameters: serum [Na^+], serum [K^+], serum urea nitrogen (SUN), serum creatinine, estimated glomerular filtration rate, urine sodium, urine potassium, urine osmolality, serum uric acid, and serum albumin, as well as demographic measures such as weight, height, age, and sex. The diagnosis of SIADH was based on the clinical diagnosis of euvolemic hyponatremia, urine [Na^+] > 30 mEq/L, urine osmolality > 300 mOsm/L, low-normal serum uric acid level (if available), and in some instances, a decrease in serum [Na^+] following isotonic saline solution infusion.

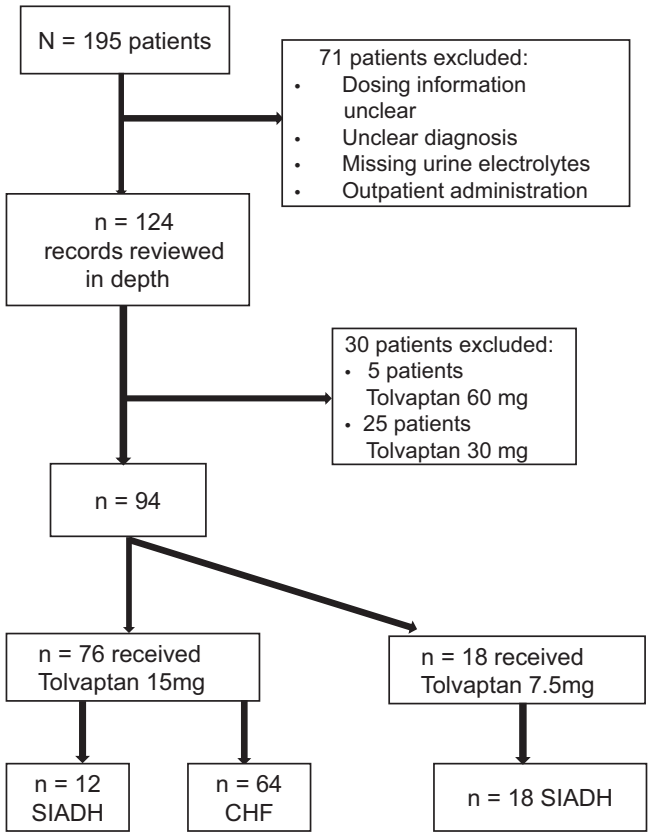

Figure 1. Patient selection for 7.5-mg tolvaptan cohort. Abbreviations: CHF, congestive heart failure; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

A total of 195 records were obtained by search with aim to examine records of patients who received 7.5 mg as the first dosing of tolvaptan. There were 71 records excluded due to other concomitant treatments (normal saline solution, salt tablets, and 3% normal saline solution) with tolvaptan use, insufficient dosing information, unclear diagnosis, insufficient laboratory data, outpatient medication administration, or administration of tolvaptan doses at intervals less than 24 hours. A total of 124 records of patients who were treated with only tolvaptan and clearly charted were reviewed in depth. Of those, 30 patients received doses of 30 and 60 mg, 76 patients received a 15-mg dose, and 18 patients received 7.5 mg of tolvaptan. All 18 patients receiving a 7.5-mg dose as treatment were patients with SIADH. Of the selected patients who received 15 mg of tolvaptan, a minority had SIADH, prompting use of Morris et al[20] data as a control group (Fig 1). All patients treated with the 7.5-mg tolvaptan dose were treated by one of the authors of this work.

Patients who received 7.5 mg of tolvaptan uniformly had their water restriction liberated and their serum [Na^+] monitored at least twice a day. If serum [Na^+] increased by >8 mEq/L in the first 24 hours, they were uniformly started on intravenous 5% dextrose in water solution infusion to match water losses to prevent additional

Table 1. Demographics of Patients in the Very Low-Dose Tolvaptan Cohort

Patient ID	History of CHF	History of Cirrhosis	History of NS	Race	Sex	Age, y	Weight, kg	Height, m
Patient 1, average of 2 administrations	Y	N	N	White	F	76	59.4	1.7
Patient 2, average of 3 administrations	N	N	N	White	F	85	53.1	1.58
Patient 3, administration 1	N	N	N	White	M	78	72.1	1.82
Patient 4, administration 1	N	N	N	White	F	81	61	1.47
Patient 5, administration 1	N	N	N	Asian	M	70	67.1	1.75
Patient 6, administration 1	N	N	N	Hispanic	M	96	35.9	1.6
Patient 7, administration 1	N	N	N	White	F	36	71	1.6
Patient 8, administration 1	N	N	Y	Asian	F	81	46.8	1.3
Patient 9, administration 1	N	N	N	White	M	79	80	1.78
Patient 10, average of 2 administrations	N	N	N	Middle Eastern	M	56	73.5	1.73
Patient 11, administration 1	N	N	N	White	F	90	55.3	1.61
Patient 12, administration 1	Y	N	N	White	M	101	62.6	1.63
Patient 13, administration 1	N	N	N	African American	M	52	133	1.78
Patient 14, administration 1	N	N	N	White	F	76	48.2	1.55
Patient 15, administration 1	N	N	N	Hispanic	F	66	48.1	1.6
Patient 16, administration 1	N	N	N	White	M	51	52.4	1.6
Patient 17, administration 1	N	N	N	Hispanic	M	48	71.7	1.61
Patient 18, administration 1	N	N	N	White	F	76	51.1	1.63
Mean ± SD or n/N (%)	2/18 (11%)	0/18 (0%)	1/18 (6%)		9/18 (50%)	72.1 ± 17.5	63.5 ± 20.9	1.6 ± 0.1

Note: Cause of hyponatremia for all patients was syndrome of inappropriate antidiuretic hormone secretion; no history of alcoholism for all patients.
Abbreviations: CHF, congestive heart failure; F, female; M, male; N, no; NS, nephrotic syndrome; SD, standard deviation; Y, yes.

Table 2. Laboratory Values for the Very Low-Dose Tolvaptan Cohort

Patient ID	Scr, mg/dL	eGFR, mL/min	SUN, mg/dL	sUA, mg/dL	sAlb, g/dL	sK^+, mEq/L	sNa^+_1, mEq/L	sNa^+_2, mEq/L	uNa^+, mEq/L	uK^+, mEq/L	Uosm, mOsm/L
Patient 1, average of 2 administrations	0.8	90	17	7	3.2	3.8	123.5	126	44	48.5	480
Patient 2, average of 3 administrations	0.7	90	17	2.1	3.7	4.2	127	130.33	59	33.3	397
Patient 3, administration 1	1.3	65	22	3.8	5	4.5	126	134	62	40.7	500
Patient 4, administration 1	0.75	75	17	2.5	3.3	4.2	121	127	36	24.4	339
Patient 5, administration 1	0.6	90	21	2.6	4	4.9	122	129	40	56.3	549
Patient 6, administration 1	0.4	90	11	1	3.3	3.7	120	126	150	36.3	538
Patient 7, administration 1	0.5	90	9	1.3	2.9	4.3	122	135	110	111.5	713
Patient 8, administration 1	1.5	33	24	5.8	3.6	4.3	123	127	31	21.8	305
Patient 9, administration 1	0.74	87	14	2.5	3.9	4.4	128	135	65	50.8	625
Patient 10, average of 2 administrations	0.63	89	27		3.4	3.9	134.5	136	79	21	278
Patient 11, administration 1	0.69	89	21		3.5	4.1	121	129	71		338
Patient 12, administration 1	0.6	80	10	3.1	2.9	4.2	121	130	67	45	433
Patient 13, administration 1	2.66	31	26	8.4	4.1	3.4	125	131	41	30	336
Patient 14, administration 1	0.5	120	6	1.1	3.9	3.5	116	122	100		371
Patient 15, administration 1	0.22	100	4	2.7	2.3	3.9	125	125	128	28	651
Patient 16, administration 1	0.7	107	9	2.1	3.1	4	114	120	70		286
Patient 17, administration 1	0.65	100	2	3	3.2	3.6	130	132	67		631
Patient 18, administration 1	0.88	85	18	2.3	3.7	3.7	127	132	88		520
No. of measurements	18	18	18	16	18	18	18	18	18	13	18
Mean ± SD	0.8 ± 0.5	83.9 ± 22.3	15.3 ± 7.6	3.21 ± 2.1	3.5 ± 0.6	4 ± 0.4	123.7 ± 4.9	129.2 ± 4.5	72.7 ± 32.4	42.1 ± 23.8	460.6 ± 137.5

Abbreviations: eGFR, estimated glomerular filtration rate (Modification of Diet in Renal Disease Study equation ml/min/1.73m^2); sAlb, serum albumin; Scr, serum creatinine; SD, standard deviation; sK^+, serum potassium; sNa^+_1, initial serum sodium; sNa^+_2, final serum sodium; sUA, serum uric acid; SUN, serum urea nitrogen; uK^+, urine potassium; uNa^+, urine sodium; uOsm, urine osmolality.

Table 3. Sodium Correction Data for the Very Low-Dose Tolvaptan Cohort

Patient ID	Delta [Na^+], mEq/L per d	D5W needed	Overcorrection >12 mEq/L
Patient 1, average of 2 administrations	2.5	N	N
Patient 2, average of 3 administrations	3.33	N	N
Patient 3, administration 1	8	Y	N
Patient 4, administration 1	6	Y	N
Patient 5, administration 1	7	Y	N
Patient 6, administration1	6	N	N
Patient 7, administration 1	13	Y	Y
Patient 8, administration1	4	N	N
Patient 9, administration 1	7	N	N
Patient 10, average of 2 administrations	1.5	N	N
Patient 11, administration 1	8	Y	N
Patient 12, administration 1	9	Y	N
Patient 13, administration 1	6	N	N
Patient 14, administration 1	6	N	N
Patient 15, administration 1	0	N	N
Patient 16, administration 1	6	N	N
Patient 17, administration 1	2	N	N
Patient 18, administration 1	5	N	N
No. of measurements	18	18	18
Mean ± SD or n/N (%)	5.6 ± 3.1	6/18 (33.3%)	1/18 (5.6%)

Note: Total number of administrations: 21, total number of patients: 18. Percentages have been rounded to 1 significant digit.
Abbreviations: D5W, 5% dextrose in water; Delta [Na^+], change in serum sodium concentration; N, no; SD, standard deviation; Y, yes.

correction of serum [Na^+]. Eighteen patients were identified who had received tolvaptan, 7.5 mg, daily. Three patients had received tolvaptan serially on more than 1 day until they achieved eunatremia. The causes of SIADH in patients were identified as idiopathic (6), malignancy (3), drug induced (3), pulmonary infections (3), and central nervous system pathology (3; Fig S2).

The raw data from Morris et al[20] (courtesy of Dr Juan Carlos Velez) was obtained to enable statistical analysis of the change in sodium values within a specific time frame in comparison with our cohort.

Statistical Analysis

Results are reported as mean ± standard deviation, and the initial and final serum sodium values were compared for statistical significance using paired *t* test. Baseline characteristics and delta sodium values between cohorts were compared using unpaired *t* test. The proportion of patients with certain baseline characteristics or achieving certain correction points were compared using Fisher exact χ^2 test (F test) with significance defined as $P < 0.05$. Data were rounded off to a maximum of 1 decimal place.

RESULTS

The total number of patients in our cohort receiving sequential tolvaptan administrations was 3 of 18 patients. Mean age of patients was 72.1 ± 17.5 years. Mean weight was 63.5 ± 20.9 kg, and mean height was 1.6 ± 0.1 m. There were 9 male and 9 female patients. Ethnicities consisted of 11 white patients, 3 Hispanic patients, 2 Asian patients, 1 African American patient, and 1 Middle Eastern patient. Two of 18 patients had a history of congestive heart failure, but they were clinically not in heart failure per charting and their clinical presentations were consistent with euvolemic hyponatremia due to SIADH. One of 18 patients had a diagnosis of nephrotic syndrome (Table 1).

As summarized in Table 2, mean laboratory values were as follows: initial serum [Na^+] (sNa^+_1), 123.7 ± 4.9 mEq/L; serum [K^+], 4. ± 0.4 mEq/L; serum SUN, 15.3 ± 7.6 mg/dL; serum creatinine, 0.8 ± 0.5 mg/dL; urine osmolality, 460.6 ± 137.5 mOsm/kg; urine [Na^+], 72.7 ± 32.4 mEq/L; urine [K^+], 42.1 ± 23.8 mEq/L; and estimated glomerular filtration rate, 83.9 ± 22.3 mL/min/1.73 m^2. Mean serum albumin level was 3.5 ± 0.6 g/dL, and mean uric acid level was 3.21 ± 2.1 mg/dL. Twenty-four hours after low-dose (7.5 mg) tolvaptan administration, mean serum [Na^+] (sNa^+_2) had increased significantly to 129.2 ± 4.5 mEq/L. Mean delta [$sNa^+_2 - sNa^+_1$] = 5.6 ± 3.1 mEq/L; $P < 0.001$. Figure S2 shows delta sodium values in the Hanna et al[17] cohort treated with 7.5 mg of tolvaptan and their change over 24 hours (sNa^+_1 and sNa^+_2).

The value of 3 mEq/L per day was previously suggested by Morris et al[20] as the threshold for efficacy. Fourteen of 18

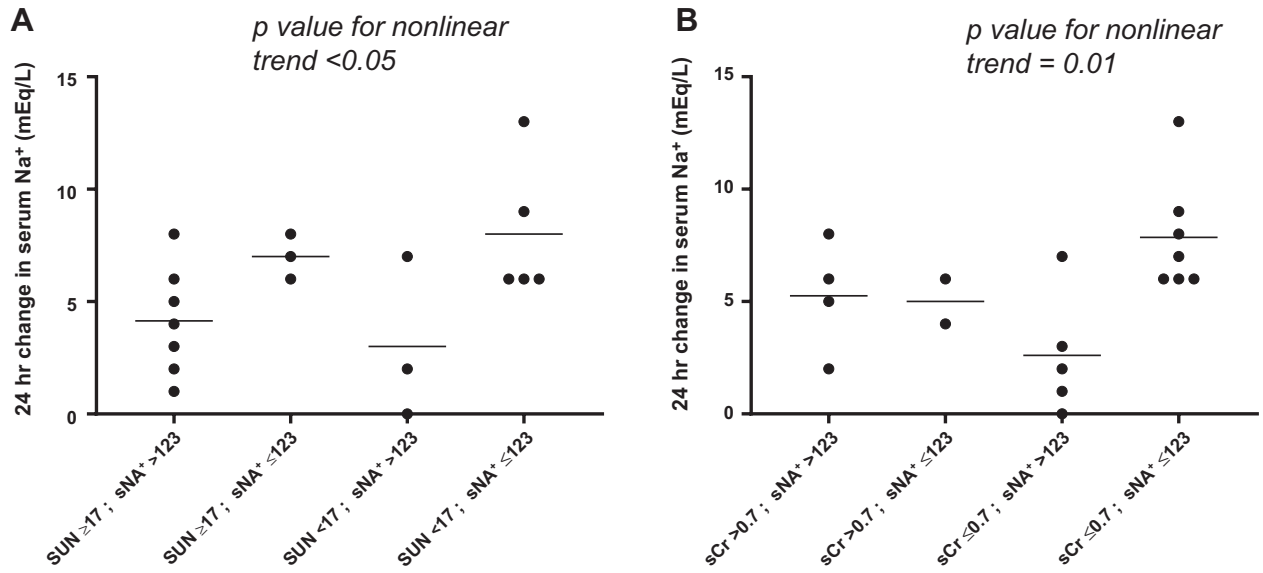

Figure 2. Distribution of changes in serum sodium (sNa^+) level 24 hours after 7.5-mg dose of tolvaptan in 18 patients with syndrome of inappropriate antidiuretic hormone secretion according to quartiles of baseline values of (A) serum urea nitrogen (SUN) and sNa^+ (above and below the median) and (B) serum creatinine (sCr) and sNa^+ (above and below the median).

patients (78% of the cohort) had a correction of ≥3 mEq/L per day. Two of 18 patients corrected serum [Na^+] by >8 mEq/L at any time during the 24 hours after the 7.5-mg tolvaptan administration. These 2 and 4 other patients (6 total) received 5% dextrose in water solution infusion (50-200 mL/h) to match their urine output rate and prevent

Table 4. Baseline Characteristics of Hanna et al and Morris et al Cohorts

Characteristic	Hanna et al[19] UCLA Cohort	Morris et al[20] Ochsner Cohort	Statistical Test Type	*P* Significance (<0.05)
N	18	28	NA	NA
Female sex	9/18 (50%)	13/28 (46.4%)	Fisher exact χ^2 test	$P = 1$
Male sex	9/18 (50%)	15/28 (53.6%)	Fisher exact χ^2 test	$P = 1$
White	11/18 (61.1%)	22/28 (78.6%)	Fisher exact χ^2 test	$P = 0.3$
African American	1/18 (5.6%)	6/28 (21.4%)	Fisher exact χ^2 test	$P = 0.2$
Idiopathic SIADH	6/18 (33%)	6/28 (21.4%)	Fisher exact χ^2 test	$P = 0.5$
Malignancy SIADH	3/18 (16.7%)	13/28 (46.4%)	Fisher exact χ^2 test	$P = 0.06$
Drug-induced SIADH	3/18 (16.7%)	2/28 (7.1%)	Fisher exact χ^2 test	$P = 0.4$
Pulmonary SIADH[a]	3/18 (16.7%)	2/28 (7.1%)	Fisher exact χ^2 test	$P = 0.4$
CNS SIADH	3/18 (16.7%)	2/28 (7.1%)	Fisher exact χ^2 test	$P = 0.4$
Postoperative SIADH	0/18 (0%)	3/28 (10.7%)	Fisher exact χ^2 test	$P = 0.3$
Age, y	72.1 ± 17.5	67.3 ± 15.3	Unpaired 2-tailed *t* test	$P = 0.3$
Weight, kg	63.5 ± 20.9	74 ± 20.3	Unpaired 2-tailed *t* test	$P = 0.1$
Height, m	1.6 ± 0.1	ND	ND	NA
BMI, kg/m^2[b]	23.7 ± 5.9	25.7 ± 4.8	Unpaired 2-tailed *t* test	$P = 0.2$
Na^+_1 initial, mEq/L	123.7 ± 4.9	120.6 ± 5.2	Unpaired 2-tailed *t* test	$P < 0.05$
Serum urea nitrogen, mg/dL	15.3 ± 7.6	12.2 ± 7.6	Unpaired 2-tailed *t* test	$P = 0.2$
eGFR (MDRD), mL/min[c]	83.9 ± 22.3	92.8 ± 26.6	Unpaired 2-tailed *t* test	$P = 0.2$
Serum uric acid, mg/dL[d]	3.2 ± 2.1	2.8 ± 2.3	Unpaired 2-tailed *t* test	$P = 0.7$
Serum potassium, mEq/L	4 ± 0.4	4.2 ± 0.6	Unpaired 2-tailed *t* test	$P = 0.2$
Urine sodium, mEq/L	72.7 ± 32.4	88.4 ± 37.9	Unpaired 2-tailed *t* test	$P = 0.2$
Urine osmolality, mOsm/L	460.6 ± 137.5	480.6 ± 130.5	Unpaired 2-tailed *t* test	$P = 0.6$

Note: Percentages have been rounded to 1 significant digit.
Abbreviations: BMI, body mass index; CNS, central nervous system; MDRD, Modification of Diet in Renal Disease; NA, not applicable; Na^+_1, initial serum sodium; ND, not done; SD, standard deviation; SIADH, syndrome of inappropriate antidiuretic hormone secretion; UCLA, University of California, Los Angeles.
[a]Nonmalignant pulmonary SIADH.
[b]Calculated from height and weight in our cohort (Table 1).
[c]MDRD Study equation data available for only our cohort.
[d]n=16 for uric acid for Hanna et al and n=10 for uric acid for Morris et al in the SIADH cohorts.

Table 5. Analysis of Summary Statistics

Characteristic	Hanna et al	Morris et al	Statistical Test Type	*P* Significance (*<0.05)
n	18	28	NA	NA
$Na^+_1 \neq Na^+_2$			Paired 2-tailed *t* test	$P < 0.001$ for both cohorts[a]
Delta Na^+ ($Na^+_2 - Na^+_1$) over 24 h[a,b]	5.6 ± 3.1	8.3 ± 6.3	Unpaired 2-tailed *t* test	$P = 0.1$
% needing D5W	(6/18) 33.3%	(5/28) 17.9%	Fisher exact χ^2 test	$P = 0.3$
% efficacy (≥3 mEq/L increase in 1 d)	14/18 (77.8%)	21/28 (75%)	Fisher exact χ^2 test	$P > 0.99$
% correcting >8 mEq/L in 1 d	2/18 (11.1%)	11/28 (39.3%)	Fisher exact χ^2 test	$P = 0.049$
% correcting 10 mEq/L in 1 d	1/18 (5.6%)	10/28 (35.7%)	Fisher exact χ^2 test	$P = 0.03$
% correcting 12 mEq/L in 1 d	1/18 (5.6%)	8/28 (28.6%)	Fisher exact χ^2 test	$P = 0.07$

Note: Percentages have been rounded to 1 significant digit.
Abbreviations: D5W, 5% dextrose water; Na^+_1, initial sodium; Na^+_2, final sodium (in 24 hours); NA, not applicable.
[a]Value = Na^+_2 [sodium at 24 hours] − Na^+_1 [initial sodium], in Morris et al.
[b]Only n=24 patients qualified for this because 4 points had terminal values at less than 24 hours.

additional correction. Morris et al[20] had 5 total patients treated with 5% dextrose in water solution. One of 18 patients had a serum [Na^+] correction of >12 mEq/L per day (total correction of 13 mEq/L in 24 hours), and 2 more corrected at exactly 8 mEq/L per day. The value of 3 mEq/L per day was previously defined by Morris et al[20] as the threshold for efficacy. Fourteen of 18 patients (78% of our cohort) thus had a correction of ≥3 mEq/L per day.

The 1 patient who overcorrected by >12 mEq/L per day after the 7.5-mg tolvaptan administration did not respond to 5% dextrose in water solution infusion, and there were no documented neurologic sequelae. As shown in Tables 2 and 3, the percentage of patients with a serum [Na^+] change rate of 8 to 10 mEq/L per day was 5.6%, 10 to 12 mEq/L per day was 0%, and >12 mEq/L per day was 5.6% (Tables 2 and 3). Correction of serum [Na^+] > 8 mEq/L per day was observed in 11.1% of our cohort. In agreement with the previous report by Morris et al[20] with full-dose tolvaptan (15 mg), we observed that patients with SIADH with the lowest baseline SUN values had higher risk for overcorrection with 7.5 mg of tolvaptan ($P < 0.05$). Similarly, in accord with Morris et al,[20] patients with lower serum [Na^+] and serum creatinine levels were more likely to exhibit a greater increase in serum [Na^+] within 24 hours after administration of very low-dose tolvaptan (7.5 mg; $P = 0.01$; Fig 2).

Analyzing the data of Morris et al,[20] the SIADH cohort treated with 15 mg of tolvaptan consisted of 28 patients, of whom 24 had data points out to 24 hours and beyond. Four others had terminal serum [Na^+] between 8 and 16 hours. Though these points could not be used for mean delta serum [Na^+] change over 24 hours (24 of 28 points used), they were used in comparing the risk for overcorrection within the first 24 hours (28 of 28 points used).

Table 4 describes the statistical comparison between baseline characteristics between our cohort that received 7.5 mg of tolvaptan and the prior study of Morris et al[20] that received 15 mg of tolvaptan. Baseline characteristics

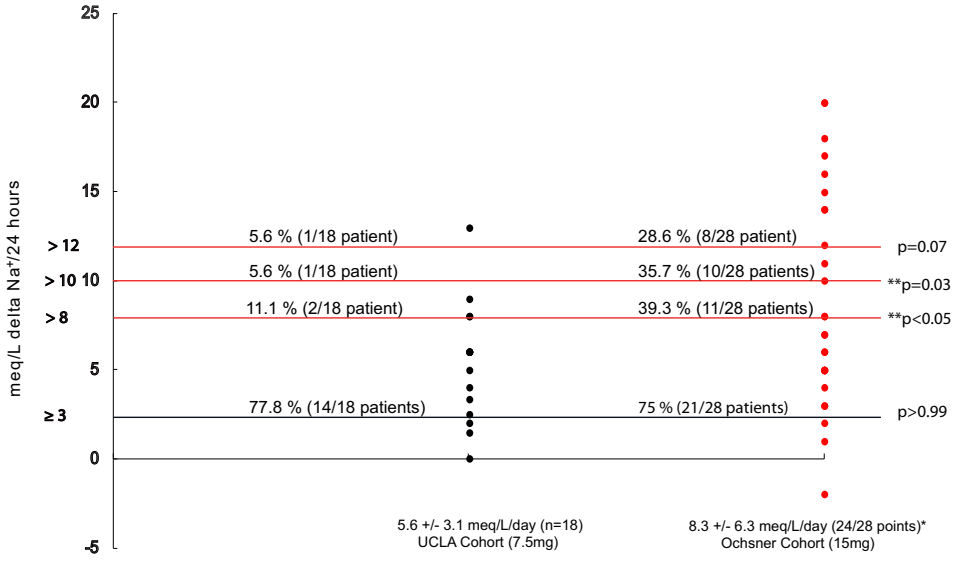

Figure 3. Comparison of delta sodium concentration ranges per day with 7.5-mg versus 15-mg tolvaptan administration in Hanna et al[19] (University of California at Los Angeles cohort) and Morris et al[20] (Ochsner cohort) in mEq/L per day.** indicates significant P value.

are not statistically significantly different, with the exception that the initial serum [Na^+] in our cohort was slightly greater than that in Morris et al.

Table 5 and Figure 3 both describe the statistical comparison of our cohort and Morris et al.[20] Efficacy was previously defined as an increase in serum [Na^+] by ≥3 mEq/L in a given day of treatment, and 14 of 18 (77.8%) patients in our cohort and 21 of 28 (75%) in the Morris et al study corrected greater than this threshold. This was determined to be statistically not different between cohorts ($P>0.991$ by F test). The average delta [Na^+] in our cohort was 5.6 ± 3.1 mEq/L per day, whereas the average delta [Na^+] in Morris et al[20] was 8.3 ± 6.3 mEq /L per day (calculated using 24 of 28 points with a 24-hour serum sodium). Both our cohort and that of Morris et al had a highly significant paired 2-tailed t test for $Na^+_1 \neq Na^+_2$ ($P < 0.0001$). An unpaired 2-tailed t test of the average delta [Na^+] per 24 hours of our cohort versus the delta [Na^+] per 24 hours of Morris et al (the 24 points with appropriate values) was not statistically significant at $P = 0.1$. The need for 5% dextrose in water solution when serum [Na^+] correction was >8 mEq/L was not statistically significant between our cohort of 6 of 18 (33.3%) patients and Morris et al of 5 of 28 (17.9%) patients ($P = 0.3$; F test).

For an increase in [Na^+] of 8 and 10 mEq/L, there was a statistically greater likelihood that the 28 patients with SIADH given 15 mg of tolvaptan in Morris et al[20] would overcorrect compared with the 18 patients with SIADH given 7.5 mg of tolvaptan in our cohort (>8 points, $P = 0.049$; >10 points, $P = 0.03$, both meeting $P < 0.05$, respectively; F tests). In the Morris et al cohort, percentages of patients who overcorrected were 28.6% at >12 mEq/L, 35.7% at >10 mEq/L, and 39.3% at >8 mEq/L per day compared with our cohort, in which the percentage of patients overcorrecting was 5.6% at >12 mEq/L, 5.6% at >10 mEq/L, and 11.1% at >8 mEq/L The delta [Na^+] of 12 mEq/L within a day was trending toward significance among the cohorts at $P = 0.07$. Figure S3 shows delta [Na^+] values in our cohort in graphical form.

DISCUSSION

Our study indicates that 7.5 mg of tolvaptan is effective in correcting hyponatremia in patients with SIADH to the recommended level within current clinical guidelines. The study also shows that there is a statistically significantly decreased tendency for overcorrection at 8 mEq/L within a day compared with the data of Morris et al,[20] who administered 15 mg per day, with a trend toward significance at [Na^+] of 12 mEq/L within a day. This equates to a difference in overcorrection between 5.5% at >12 mEq/L, 5.5% at >10 mEq/L, 11.1% at >8 mEq/L in our cohort, and 28.6% at >12 mEq/L, 35.7% at >10 mEq/L, and 39.3% at >8 mEq/L per day in the Morris et al cohort. It is important to note that the slightly higher starting sNa^+_1 in our cohort versus Morris et al may have contributed to the lower rate of overcorrection observed.

In addition to the study of Morris et al,[20] overcorrection with SIADH has been established as a concern. In Verbalis et al,[29] overcorrection was found to occur in 10.2% of patients with SIADH who were treated with diverse therapies. Park et al[30] recently reproduced the overcorrection with use of tolvaptan on the first day of therapy in patients with SIADH as compared with patients with congestive heart failure. However, the SIADH cohort was treated with a variable dose as compared with Morris et al.[20]

Strict water restriction may increase the risk for overcorrection with V2 antagonist therapy, and serum [Na^+] should be checked frequently depending on risk for overcorrection. In low-risk cases, every 8 to 12 hours is generally acceptable, more frequently in cases at higher risk for osmotic demyelination syndrome or overcorrection with vaptan therapy.[22] We have previously recommended that patients who receive 7.5 mg of tolvaptan should have urine osmolality and serum [Na^+] checked.[22] If a sufficient response is noted, laboratory test results should be monitored. If an insufficient response is noted with urine osmolality remaining >300 mOsm, a repeat dosing of 7.5 mg of tolvaptan can be used.[22] It is our recommendation that in patients with SIADH, 7.5 mg of tolvaptan should be used as the starting dose for therapy with V2 antagonists, particularly in patients with high risk factors for osmotic demyelination syndrome and/or rapid overcorrection.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1: Risk factors for osmotic demyelination and serum sodium concentration overcorrection.

Figure S2: Causes of syndrome of inappropriate diuresis/SIADH in very low-dose tolvaptan cohort.

Figure S3: Na^+1 and Na^+2 (initial and terminal sodium concentrations) in Hanna et al cohort treated with 7.5 mg of tolvaptan.

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