Rapidity of Correction of Hyponatremia Due to Syndrome of Inappropriate Secretion of Antidiuretic Hormone Following Tolvaptan

Jesse H. Morris, Nicole M. Bohm, Branden D. Nemecek, Rachel Crawford, Denise Kelley, Bhavna Bhasin, Paul J. Nietert, and Juan Carlos Q. Velez

Background: Tolvaptan effectively corrects hyponatremia due to the syndrome of inappropriate secretion of antidiuretic hormone (SIADH), but undesired overcorrection can occur. We hypothesized that pretherapy parameters can predict the rapidity of response to tolvaptan in SIADH.

Study Design: Multicenter historical cohort study.

Setting & Participants: Adults with SIADH or congestive heart failure (CHF) treated with tolvaptan for a serum sodium concentration ≤ 130 mEq/L at 5 US hospitals.

Predictors: Demographic and laboratory parameters.

Outcomes: Rate of change in serum sodium concentration.

Measurements: Spearman correlations, analysis of variance, and multivariable linear mixed-effects models.

Results: 28 patients with SIADH and 39 patients with CHF treated with tolvaptan (mean baseline serum sodium, 120.6 and 122.4 mEq/L, respectively) were studied. Correction of serum sodium concentration > 12 mEq/L/d occurred in 25% of patients with SIADH compared to 3% of those with CHF ($P < 0.001$). Among patients with SIADH, the increase in serum sodium over 24 hours was correlated with baseline serum sodium concentration ($r = -0.78$; $P < 0.001$), serum urea nitrogen concentration (SUN; $r = -0.76$; $P < 0.001$), and estimated glomerular filtration rate ($r = 0.58$; $P = 0.01$). Baseline serum sodium and SUN concentrations were identified as independent predictors of change in serum sodium concentration in multivariable analyses. When patients were grouped into 4 categories according to baseline serum sodium and SUN median values, those with both low baseline serum sodium (≤121 mEq/L) and low baseline SUN concentrations (≤10 mg/dL) exhibited a significantly greater rate of increase in serum sodium concentration (mean 24-hour increase of 15.4 mEq/L) than the other 3 categories ($P < 0.05$). Among patients with CHF, only baseline SUN concentration was identified as an independent predictor of change in serum sodium concentration over time.

Limitations: Lack of uniformity in serial serum sodium concentration determinations and documentation of water intake.

Conclusions: Baseline serum sodium and SUN values are predictive of the rapidity of hyponatremia correction following tolvaptan use in SIADH. We advise caution when dosing tolvaptan in patients with both low serum sodium and SUN concentrations.

Complete author and article information provided before references.

Correspondence to J.C.Q. Velez (juancarlos.velez@ochsner.org)

Am J Kidney Dis. 71(6): 772-782. Published online February 22, 2018.

doi: 10.1053/j.ajkd.2017.12.002

Overly rapid correction of chronic hyponatremia is an undesired event that can potentially lead to irreversible neurologic damage resulting from brain dehydration due to an adaptive loss of intracellular osmoles in the brain of chronically hyponatremic individuals.[1,2] Cases of osmotic demyelination syndrome (ODS) have been reported in association with administration of hypertonic[3-6] or isotonic saline solution.[7,8] Vasopressin receptor antagonists are now available to treat hyponatremia. Conivaptan, a nonselective V_{1a}/V_2 receptor antagonist, is available by intravenous route, and tolvaptan, a selective V_2 receptor antagonist, is available as an oral formulation.[9] Although no cases of ODS have been directly and solely attributed to a vasopressin receptor antagonist, a case of ODS with concomitant use of tolvaptan and diuretics was recently reported,[10] and cases in patients concomitantly treated with tolvaptan and hypertonic saline solution have been submitted to the US Food and Drug Administration.[11] Therefore, it is critical to recognize patients at increased risk for rapid correction of hyponatremia when they are treated with tolvaptan.

Editorial, p. 763

Cases of euvolemic hyponatremia caused by the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) exhibit a more rapid and larger increase in serum sodium concentration in response to tolvaptan than those with hypervolemic hyponatremia.[12] Overcorrection of hyponatremia has been reported in patients with SIADH treated with tolvaptan.[13-15] Further illustrating this phenomenon, reports of requirement of administration of intravenous 5% dextrose in water (D5W) solution following treatment with a vasopressin receptor antagonist to revert overcorrection of SIADH-induced hyponatremia have emerged.[14-16]

We sought to examine whether baseline demographic, clinical, or laboratory characteristics of treated patients could influence the magnitude of the response to tolvaptan in SIADH. We also analyzed a cohort of patients with

congestive heart failure (CHF) treated with tolvaptan for comparison. Because our previous report in conivaptan-treated patients with SIADH revealed a significant correlation between the increase in serum sodium concentration and glomerular filtration rate (GFR) and serum urea nitrogen (SUN) values,[16] we hypothesized that kidney function parameters may predict the magnitude of the increase in serum sodium concentration following tolvaptan administration in patients with SIADH.

Methods

Study Design

We conducted a multicenter retrospective review of medical records to identify patients treated with oral tolvaptan between 2010 and 2015. The study protocol was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board at the Medical University of South Carolina Hospital, as well as each of the other participating sites: Wake Forest Baptist Medical Center, Beaufort Memorial Hospital, University of Florida Health Jacksonville, and Duquesne University Hospital. Data were collected by each hospital biomedical informatics center and condensed from the 5 sites for analysis centrally at Medical University of South Carolina. Patients were identified based on documentation of tolvaptan administration during a hospitalization from a centralized pharmacy data warehouse at each participating institution. All data were deidentified; thus, the need for informed consent was waived.

Study Population

The study population consisted of hospitalized adult patients 18 years or older treated with an initial daily dose of 15 mg of tolvaptan. Eligible patients had a diagnosis of moderate to severe hypo-osmolal hyponatremia, defined as serum sodium concentration ≤ 130 mEq/L and serum osmolality ≤ 280 mOsm/kg, caused by either SIADH (defined as euvolemic hyponatremia with inappropriate urinary concentration, ie, urine osmolality > 100 mOsm/kg and urine sodium excretion > 20 mEq/L[15-20]), or by CHF (defined as hypervolemic hyponatremia with echocardiographic evidence of systolic or diastolic dysfunction and urine sodium excretion < 20 mEq/L for those not taking diuretics). Each patient needed documented failure to correct hyponatremia despite 24 or more hours of free water restriction (≤1 L/d). To reduce the risk for rapid correction, fluid restriction was discontinued at the time of initiation of tolvaptan therapy. Exclusion criteria included initial daily dose of tolvaptan different than 15 mg (ie, 3.75, 7.5, or 30 mg); concomitant treatment with desmopressin, diuretics, demeclocycline, hypertonic or normal saline solution, other sodium/water-based therapies such as D5W, sodium phosphate, sodium chloride, or sodium bicarbonate; or inability to conclusively diagnose SIADH or CHF based on insufficient or inconsistent data. For patients who were started on water- or sodium-based therapies after the initial tolvaptan administration, data were censored from the beginning of the administration of the water- or sodium-based therapy and onward. The purpose of censoring data from the initiation of an intervention to slow the rate of correction and onward was not to bias results toward overcorrection, but rather to specifically analyze the sole effect of tolvaptan on the rate of correction and not the effect of combined therapies, such as tolvaptan plus intravenous D5W solution. Patients with hypervolemic hyponatremia from CHF were allowed to be on diuretic therapy for inclusion.

Assessments

We collected demographic and clinical data at baseline and throughout the first 24 hours following tolvaptan administration. Laboratory parameters included serum creatinine, SUN, serum uric acid, serum potassium, serum sodium and osmolality, and urine sodium and osmolality. Baseline parameters were considered those obtained within 4 hours before the first administered dose of tolvaptan. Kidney function was estimated using the 4-variable isotope-dilution mass spectrometry–traceable Modification of Diet in Renal Disease (MDRD) Study equation[21] or the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[22] Medical records were manually reviewed to ascertain the presumed cause of hyponatremia and documentation of prior failure to correct hyponatremia with fluid restriction.

Study End Points

The primary end point was absolute change in serum sodium concentration during the first 24 hours following the first dose of tolvaptan. Rapid correction of hyponatremia was defined as an increase in serum sodium concentration > 12 mEq/L after 24 hours of therapy.[18] A more conservative definition of rapid correction (>8 mEq/L in 24 hours) was also examined.

Statistical Analysis

Because as many as 10 serum sodium measurements were obtained for study participants during the 24-hour period (at baseline and 2, 4, 6, 8, 10, 12, 16, 20, and 24 hours), linear mixed-effects models (LMEMs) were used to conduct multivariable repeated-measures analyses.[23,24] The LMEMs allowed us to determine the extent to which any demographic, clinical, or laboratory characteristics were independently associated with change from baseline in serum sodium concentration during the 24-hour period. They also allowed us to compare slope estimates over time between the 2 cohorts using a 2-sample t test framework based on slope estimates and their standard errors. LMEMs incorporated random participant effects with an autoregressive covariance structure to account for within-participant correlation. Backwards model selection was used to identify the factors most strongly correlated with change in serum sodium concentration. In addition, analyses were conducted to test whether there were significant interactions between the identified factors and time.