CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

Diagnosing and Treating the Syndrome of Inappropriate Antidiuretic Hormone Secretion

Joseph G. Verbalis, MD,[a] Arthur Greenberg, MD,[b] Volker Burst, MD,[c] Jean-Philippe Haymann, MD,[d] Gudmundur Johannsson, MD, PhD,[e] Alessandro Peri, MD, PhD,[f] Esteban Poch, MD,[g] Joseph A. Chiodo, III, PharmD,[h] Jiten Dave, MD[i]

[a]Division of Endocrinology and Metabolism, Georgetown University Medical Center, Washington, DC; [b]Duke University Medical Center, Durham, NC; [c]Department 2 of Internal Medicine and Center for Molecular Medicine, University Hospital of Cologne, Cologne, Germany; [d]Hôpital Tenon, Paris, France; [e]Department of Endocrinology, Institute of Medicine, University of Göteborg and Sahlgrenska University Hospital, Göteborg, Sweden; [f]University of Florence, Florence, Italy; [g]Nephrology Department, Hospital Clinic, IDIBAPS, University of Barcelona, Barcelona, Spain; [h]Otsuka America Pharmaceuticals, Inc, Princeton, NJ; [i]Otsuka Pharmaceuticals Europe Ltd, Wexham, United Kingdom.

ABSTRACT

BACKGROUND: The syndrome of inappropriate antidiuretic hormone secretion is the most common cause of hyponatremia in clinical practice, but current management of hyponatremia and outcomes in patients with syndrome of inappropriate antidiuretic hormone secretion are not well understood. The objective of the Hyponatremia Registry was to assess the current state of management of hyponatremia due to syndrome of inappropriate antidiuretic hormone secretion in diverse hospital settings, specifically which diagnostic and treatment modalities are currently used and how rapidly and reliably they result in an increase in serum sodium concentration ($[Na^+]$). A secondary objective was to determine whether treatment choices and outcomes differ across the United States and the European Union.

METHODS: The Hyponatremia Registry recorded selected diagnostic measures and use, efficacy, and outcomes of therapy for euvolemic hyponatremia diagnosed clinically as syndrome of inappropriate antidiuretic hormone secretion in 1524 adult patients with $[Na^+] \leq 130$ mEq/L (1034 from 146 US sites and 490 from 79 EU sites). A subgroup of patients with more rigorously defined syndrome of inappropriate antidiuretic hormone secretion via measurement of relevant laboratory parameters was also analyzed.

RESULTS: The most common monotherapy treatments for hyponatremia in syndrome of inappropriate antidiuretic hormone secretion were fluid restriction (48%), isotonic (27%) or hypertonic (6%) saline, and tolvaptan (13%); 11% received no active agent. The mean rate of $[Na^+]$ change (mEq/L/d) was greater for all active therapies than no active treatment. Hypertonic saline and tolvaptan produced the greatest mean rate of $[Na^+]$ change (interquartile range, both 3.0 [6.0] mEq/L/d) compared with lower interquartile range rates of $[Na^+]$ change for isotonic saline (1.5 [3.0] mEq/L/d) and fluid restriction (1.0 [2.3] mEq/L/d). The general pattern of responses was similar in both the US and EU cohorts. At discharge, $[Na^+]$ was <135 mEq/L in 75% of patients and ≤ 130 mEq/L in 43% of patients. Overly rapid correction occurred in 10.2% of patients.

CONCLUSIONS: Current treatment of hyponatremia in syndrome of inappropriate antidiuretic hormone secretion often uses therapies with limited efficacy; the most commonly chosen monotherapy treatments, fluid restriction and isotonic saline, failed to increase the serum $[Na^+]$ by ≥ 5 mEq/L in 55% and 64% of monotherapy treatment episodes, respectively. Appropriate laboratory tests to diagnose syndrome of inappropriate antidiuretic hormone secretion were obtained in $<50\%$ of patients; success rates in correcting hyponatremia were significantly higher when such tests were obtained. Few outcome differences were found between the United States and the European Union. A notable exception was hospital length of stay; use of tolvaptan was associated with significantly shorter length of stay in the European Union but not in the United States. Despite the availability of effective therapies, most patients with syndrome of inappropriate antidiuretic hormone secretion were discharged from the hospital still hyponatremic.

 • *The American Journal of Medicine (2016) 129, 537.e9-537.e23*

KEYWORDS: Fluid restriction; Hypertonic saline; Hyponatremia; Isotonic saline; Syndrome of inappropriate antidiuretic hormone secretion; Tolvaptan

0002-9343/$ -see front matter © 2016 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.amjmed.2015.11.005

Hyponatremia is the most common electrolyte abnormality, affecting up to 30% to 42% of hospitalized patients across numerous studies throughout the world over the last several decades.[1,2] Hyponatremia is important because it is associated with worse clinical outcomes across the entire range of inpatient care[3] and with increased hospital costs and readmission rates.[4,5] In every disease studied, hyponatremia has been found to be an independent risk factor for increased mortality.[6] Chronic hyponatremia has been linked to impaired gait and balance, falls, osteoporosis, and increased fracture rates,[7-10] although its causal role for these associations remains unproven.[11] Despite the widespread clinical impression that correction of hyponatremia is beneficial, evidence-based data demonstrating the clinical benefit of correction of hyponatremia are limited,[7,12-14] and treatment practices vary widely.

The multinational Hyponatremia Registry assessed the current state of treatment of euvolemic and hypervolemic hyponatremia in diverse, real-world hospital settings. The Registry was designed to determine which diagnostic and treatment modalities are currently used, how effective they are, and how rapidly and reliably they result in an increase in serum sodium concentration ($[Na^+]$). A recent publication summarized the results of the Hyponatremia Registry for all hyponatremic patients[15]; the current report focuses on the more homogeneous subgroup of patients with the syndrome of inappropriate antidiuretic hormone secretion. A secondary objective is to determine whether treatment choices and outcomes for syndrome of inappropriate antidiuretic hormone secretion differ across the United States and the European Union.

CLINICAL SIGNIFICANCE

- Hyponatremia in 1524 hospitalized patients with syndrome of inappropriate antidiuretic hormone secretion was not diagnosed or treated successfully in more than half the cases studied across both the United States and the European Union.
- Despite the availability of effective therapies, most patients with syndrome of inappropriate antidiuretic hormone secretion were discharged still hyponatremic.
- Success rates in correcting hyponatremia were significantly higher when appropriate laboratory tests were obtained and pharmacologic therapies were used.

MATERIALS AND METHODS

Study Plan

The study design has been described in detail by Hauptman et al.[16] Patients with euvolemic or hypervolemic hyponatremia were enrolled from 146 US sites, and patients with euvolemic hyponatremia were enrolled from 79 EU sites. For the present publication, only patients initially assessed as clinically euvolemic by the treating physicians were analyzed. At each site, approval was sought from the appropriate research ethics review boards as required. After informed consent or waiver, investigators recorded patient data. The study was exclusively observational: No diagnostic or treatment protocols were imposed.

Inclusion and Exclusion Criteria

To ensure that hyponatremia was clinically significant, the Registry required an entry $[Na^+] \leq 130$ mEq/L. Patients were excluded if they were aged <18 years, hypovolemic, using an investigational agent or device, hyperglycemic enough to interfere with assessment of $[Na^+]$, or receiving renal replacement therapy while hyponatremic. Euvolemia and a clinical diagnosis of syndrome of inappropriate antidiuretic hormone secretion were determined by the treating physician's clinical assessment. A complete listing of inclusion and exclusion criteria is found in **Supplemental Table 1**, available online.

Data Collection

Principal data collection items are as recently described by Greenberg et al.[15]

Adjudication

To ensure data consistency, data from patients who met prespecified review thresholds were subject to review by 2 members of the study steering committee. Discrepancies were resolved by review by the committee co-chairmen. Prespecified criteria triggering adjudication have been published.[16] Although it was not originally a specified exclusion criterion, we subsequently excluded any patient receiving a thiazide at the time the treating physician made a diagnosis of syndrome of inappropriate antidiuretic hormone secretion, because it would be difficult to ensure that such patients were not in fact hypovolemic,[17] and diuretic use is generally considered to be an exclusion to the proper diagnosis of syndrome of inappropriate antidiuretic hormone secretion.[18] This decision was made before data analysis.

Subgroup Analysis

Because initial data analysis showed that many patients with a clinical diagnosis of syndrome of inappropriate antidiuretic hormone secretion did not have measurement of key laboratory parameters necessary to confirm this diagnosis, a subgroup was created to better ensure the veracity of this diagnosis. This cohort consisted of only those patients with a clinical diagnosis of syndrome of inappropriate antidiuretic hormone secretion who also met the following criteria: urine osmolality measured and found to be >100 mOsm/kg H_2O; urine $[Na^+]$ measured and found to be ≥ 30 mmol/L; if measured, thyroid-stimulating hormone <10 mIU/mL; if done, adrenocorticotropic hormone stimulation test normal (unstimulated or stimulated cortisol level ≥ 18 ug/dL).