CLINICAL RESEARCH STUDY

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Risk of Thiazide-induced Hyponatremia in Patients with Hypertension

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ABSTRACT

BACKGROUND: Although hyponatremia is a well-recognized complication of treatment with thiazide diuretics, the risk of thiazide-induced hyponatremia remains uncertain in routine care.

METHODS: We conducted a retrospective cohort study using a multicenter clinical research registry to identify 2613 adult outpatients that were newly treated for hypertension between January 1, 2000 and December 31, 2005 at 2 teaching hospitals in Boston, Massachusetts, and followed them for up to 10 years.

RESULTS: Two hundred twenty patients exposed to ongoing thiazide therapy were compared with 2393 patients who were not exposed. In the exposed group, 66 (30%) developed hyponatremia (sodium ≤130 mmol/L). The adjusted incidence rate of hyponatremia was 140 cases per 1000 person-years for patients treated with thiazides, compared with 87 cases per 1000 person-years in those without thiazides. Patients exposed to thiazides were more likely to develop hyponatremia (adjusted incidence rate ratio, 1.61; 95% confidence interval [CI], 1.15-2.25). There was no significant difference in the risk of hospitalizations associated with hyponatremia (adjusted rate ratio, 1.04; 95% CI, 0.46-2.32) or mortality (adjusted rate ratio, 0.41; 95% CI, 0.12-1.42). The number needed to harm (to result in one excess case of incident hyponatremia in 5 years) was 15.02 (95% CI, 7.88-160.30).

CONCLUSIONS: Approximately 3 in 10 patients exposed to thiazides who continue to take them develop hyponatremia.

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KEYWORDS: Hypertension; Hyponatremia; Incidence; Thiazide diuretics

One of the most important treatment decisions for hypertension is selecting a drug class for initial therapy. Thiazide and thiazide-like diuretics (hereafter collectively referred to as "thiazide diuretics") are widely recommended as first-line therapy for uncomplicated hypertension.[1-3] However, even with the global adoption of thiazide diuretics into practice and over half a century of experience with these medications, our knowledge of some of the common side effects of thiazides remains limited.[4]

Hyponatremia represents a well-recognized potential complication of thiazides that is linked to increased morbidity, and may have costly implications.[5-9] However, previous observational studies have not been designed to estimate the incidence of hyponatremia in unselected patients.[10,11] Furthermore, clinical trial data may underestimate significantly the risk of adverse drug events encountered in routine care.[12-14] As such, current literature offers limited guidance on the comparative risks between thiazides and other antihypertensive drugs in everyday practice.

Guidelines have called for more research about the adverse effects of commonly prescribed antihypertensive drugs.[5] Therefore, we performed this study to characterize the risk of hyponatremia and associated hospitalizations in patients treated with thiazides compared with those receiving alternative antihypertensive therapy. We focused on adult patients in the outpatient setting because this group accounts for the majority of patients receiving thiazides.

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METHODS

This study was approved by the Institutional Review Board at Partners Healthcare.

Study Design and Population

We designed a retrospective cohort study to evaluate the occurrence of hyponatremia in patients newly treated for hypertension through the Research Patient Data Registry—a database specifically designed for research and quality improvement purposes that serves as a central warehouse of clinical data of over 1.8 million patients. The database contains information on patient demographics, diagnoses, procedures, prescriptions, inpatient and outpatient encounters, health care providers, and laboratory results. Using this registry, we identified all adult outpatients with a diagnosis of hypertension between the dates January 1, 2000 and December 31, 2005 encountered at 2 academic hospitals and their affiliated clinics: the Brigham and Women's Hospital and Massachusetts General Hospital. These centers provide primary and tertiary care to an ethnically and socioeconomically diverse population within eastern Massachusetts.

CLINICAL SIGNIFICANCE

- The relative risk of hyponatremia among patients treated with thiazide diuretics is approximately 60% higher than patients on alternative antihypertensive therapy.
- The risk of thiazide-induced hyponatremia persists even up to 10 years of treatment.
- The number needed to harm to result in one excess case of hyponatremia in 5 years is approximately 15.

We defined the first date that a prescription was issued for an antihypertensive medication during the study interval to be the index date. We employed a new user design,[15] and excluded all patients that received any antihypertensive medication prescription in the 3 years before the index date from the study, reasoning that the remaining patients were treatment-naïve. We further excluded patients with hyponatremia before the index date (using laboratory data extending from August 1, 1988 onward), or if they died within the first 30 days of enrollment. Of those remaining, patients were defined as "thiazide-exposed" if their initial prescription was for hydrochlorothiazide, chlorthalidone, indapamide, bendroflumethiazide, metolazone, methyclothiazide, chlorothiazide, trichlormethiazide, or a combination pill containing any of these; "non-thiazide-exposed" patients were those that received an angiotensin-converting enzyme (ACE) inhibitor, angiotensin II receptor blocker, beta-adrenergic blocker, or calcium channel blocker as initial antihypertensive therapy. Patients receiving another agent as first-line therapy (eg, clonidine, hydralazine) were not considered for cohort inclusion.

Subjects were followed from their index date until first occurrence of hyponatremia, death, or December 31, 2009 (whichever came first), providing for a maximum follow-up of 10 years. To focus on specific treatment effects in our final cohort, patients were included only if they continued to receive antihypertensive prescriptions throughout the follow-up period. Among those in the "thiazide-exposed" group, only patients that had evidence of active treatment with thiazides up to and including the final 90 days of follow-up (ie, "current" users) were included. Likewise, a similar restriction was placed on the patients in the "non-thiazide-exposed" group. Additionally, "non-thiazide-exposed" patients were included only if they never received any prescription for a thiazide during the entire study period.

Outcomes

The primary outcome was the first occurrence of hyponatremia, defined as the first sodium $\leq$130 mmol/L from either an inpatient or outpatient blood collection. This threshold was chosen so that we would classify most biochemically significant cases of hyponatremia but also include fewer cases of mild (and probably clinically insignificant) hyponatremia. We used laboratory data for outcome ascertainment because diagnostic billing codes greatly underestimate the occurrence of hyponatremia.[16,17] We further classified the severity of hyponatremia according to the following categories: moderate (125-130 mmol/L), severe (120-124 mmol/L), and very severe ($<$120 mmol/L).[18] Secondary outcomes of interest were total number of hospitalizations associated with hyponatremia, total number of hospitalizations from any cause, and mortality. Hospitalizations were defined as any inpatient admission lasting at least 48 hours. Admissions associated with hyponatremia were hospitalizations with concurrent laboratory evidence of hyponatremia on the same day as admission. Mortality was determined from the Social Security Death Index.

Baseline Characteristics

The following baseline data were retrieved for each patient: sex, age, ethnicity, comorbidities (identified through International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] diagnosis codes), and prescriptions. Active treatment for nonantihypertensive medications was defined as a prescription within 120 days before the index date. The Charlson comorbidity index was calculated using the enhanced ICD-9-CM method.[19]

Analyses

Baseline characteristics between treatment groups were compared using Fisher's exact test or chi-squared test for discrete variables, and the Student's *t* test or Wilcoxon rank-sum test for continuous variables where appropriate. The occurrence of each outcome was determined according to exposure