Thiazide-Associated Hyponatremia: Clinical Manifestations and Pathophysiology

Edward J. Filippone, Mohammed Ruzieh, and Andrew Foy

Hyponatremia can complicate thiazide use in a minority of susceptible individuals and can result in significant morbidity and even mortality. Risk factors for thiazide-associated hyponatremia include age, female sex, and possibly low body mass. A genetic susceptibility has recently been uncovered. Although frequently developing early after thiazide treatment initiation, many cases of hyponatremia present after months or years of use. Many cases are asymptomatic or have mild symptoms, but seizures and/or coma may develop, especially in those with acute onset. The pathophysiology is incompletely understood and includes some combination of excessive fluid intake, cation (sodium and potassium) depletion, osmotic inactivation of sodium, and reduced ability to excrete free water. Reduced distal delivery of filtrate, reduced solute load (urea), direct inhibition of the sodium-chloride cotransporter, and increased collecting duct permeability to water mediated by some combination of antidiuretic hormone, prostaglandins, and thiazides themselves may contribute to this diluting defect. The predominant pathophysiologic mechanism(s) varies from patient to patient. The cornerstone of therapy is cessation of thiazide use, cation repletion, and oral fluid restriction. If severely symptomatic, 3% saline solution may be indicated. Overly rapid correction of chronic hyponatremia must be avoided in all cases.

Introduction

Hydrochlorothiazide, as well as other thiazides and thiazide-like diuretics including chlorthalidone, indapamide, and metolazone—herein referred to collectively as thiazides—are widely prescribed for the treatment of hypertension and calcium nephrolithiasis. Hyponatremia in patients receiving thiazides has been well described, occurring in possibly 5% to 10% of hospitalized patients, with reports as high as 30%. Rodenburg et al compared 3,556 outpatients prescribed thiazides with 9,769 unexposed participants and found nearly 5-fold increased risk for the development of any degree of hyponatremia and 8-fold increase in risk for more severe hyponatremia (sodium ≤ 125 mmol/L). Many other studies confirm this association. However, in contrast, hyponatremia is not mentioned as a specific adverse event in some large hypertension trials using thiazides or in studies of thiazide use in nephrolithiasis, possibly because hyponatremia was not specifically assessed.

The 2 major electrolyte abnormalities associated with thiazides are hypokalemia and hyponatremia. Reduction of serum potassium level is a nearly universal effect of thiazides; reduction of serum sodium level is not, but occurs in only a minority of susceptible individuals. However, surprisingly, more patients may develop frank hyponatremia (sodium < 135 mmol/L) than frank hypokalemia (potassium < 3.5 mmol/L). By these definitions, one study found that of 950 outpatients prescribed a thiazide, 13.7% had hyponatremia compared with 8.5% with hypokalemia. Whereas the decrease in serum potassium level and hypokalemia are dose dependent, data are conflicting regarding the dose-dependency of hyponatremia. As described later in this article, hyponatremia represents a state of excess total-body water (TBW) relative to total-body sodium and potassium. Most commonly this results from impaired ability to excrete excess water due to reduced glomerular filtration, enhanced proximal tubular reabsorption of filtrate, and/or inability to maximally dilute the urine, the latter typically resulting from osmotically inappropriate vasopressin (antidiuretic hormone [ADH]) release. Given that ADH is involved in the vast majority of cases of hyponatremia with preserved glomerular filtration rate (GFR), the usual clinical approach is to determine the presence of a hemodynamic cause for ADH release (baroreceptor mediated) versus the syndrome of inappropriate ADH secretion (SIADH) by assessing extracellular fluid volume. Either volume depletion or volume overload indicates a hemodynamic cause for ADH release, and euvoolemia suggests SIADH.

When a euvoletic patient receiving a thiazide manifests hyponatremia, it should be termed thiazide-associated hyponatremia (TAH). The thiazide may be directly responsible (Box 1), termed thiazide-induced hyponatremia by the Hyponatremia Registry, which encompasses more than 5,000 patients with serum sodium levels ≤ 130 mmol/L. Overall, 1,524 were considered to have SIADH compared with 477 with TAH. Of those with TAH, 118 were considered to have thiazide-induced hyponatremia based on criteria outlined in Box 1. Because this distinction can only be made with certainty in retrospect, we refer to all cases of hyponatremia developing in a patient receiving a thiazide as TAH. Hence, TAH occurs in a heterogeneous group of patients, and thiazides may not be directly responsible in all instances. This narrative review discusses the clinical features and pathophysiology of TAH.

Clinical Features

Barber et al performed a systematic review and meta-analysis of 52 case series and 49 case reports of TAH.
Box 1. Criteria for Diagnosis of Thiazide-Induced Hyponatremia

- Euvolemia by clinical assessment
- Improvement following cessation of thiazide treatment (by 3 mEq/L in 1 d or 5 mEq/L in 2 d)
- No significant improvement before cessation of thiazide use (unless specifically treated, eg, with 3% saline solution, urea, or a vaptan)
- No recurrence after resolution in the absence of a thiazide

*Note: Time course for resolution is variable. It can be abrupt or take days or even weeks to completely resolve but should not recur.*

Based on an algorithm of the Hyponatremia Registry.26

published through October 1, 2013. Patients were typically elderly, with a mean age of 75 years (pooled estimate based on meta-analysis of 36 studies comprising 2,840 patients), frequently female (79%; based on 43 studies, 3,269 patients), and with a normal body mass index (25 kg/m²; based on 2 studies, 2,025 patients). Mean time to TAH since initiation of therapy was 19 days (based on 19 studies, 446 patients). Common symptoms included falls (48%), fatigue (46%), weakness (45%), confusion (44%), nausea (36%), vomiting (35%), and dizziness, seizures, and loss of consciousness, with marked heterogeneity. Various thiazides and thiazide-like drugs were implicated. Other common medications included renin-angiotensin system blockers, nonsteroidal anti-inflammatory drugs, and antidepressants. Mean serum sodium level was 116 mmol/L, with mild hypokalemia (mean potassium, 3.3 mmol/L), normal GFR (mean glomerular filtration rate, 64 mmol/L), and elevated urinary sodium excretion (64 mmol/L) and osmolarity (402 mOsm/L).

Although median time to the development of hyponatremia was 19 days in this meta-analysis, with many developing it in less than 2 weeks, TAH can develop months to years after initiation. For example, in one study, the median time was 1.75 years.1 In another study of diuretic-associated hyponatremia (75% thiazide based), 45% were on therapy for more than 6 months, and 37%, for more than 1 year.12 In contrast, hyponatremia may rapidly develop to severe levels in 1 to 2 days.13-15

Burst et al10 recently reported data from the Hyponatremia Registry involving 477 hospitalized patients with TAH. Similar to the meta-analysis, median age was 75 years, >80% were female, median serum sodium level was 121 mEq/L, and median serum creatinine level was 0.81 mg/dL. More than 50% were receiving other potentially hyponatremia-inducing medications.

Female sex was often found to be a significant risk factor for TAH. One potential explanation may be greater expression of the thiazide-sensitive sodium chloride cotransporter (NCC) in females. A greater density of NCC can be demonstrated in female rats compared with males, as well as a greater response of urinary sodium and chloride to maximal dosing.16 Ovariectomy in the rat has also been observed to significantly decrease the distal tubule apical membrane complexity (microprojections) and density of NCC, an effect restored by long-term estrogen exposure.17 Therefore, inhibition of NCC by thiazides may produce relatively greater sodium loss in females compared with males. Additionally, in response to more significant volume depletion from greater sodium loss, free-water clearance may be more impaired in females through reduced distal delivery of filtrate and/or greater ADH release (see the following).

Pathophysiology

It has been known for 60 years that serum sodium concentration ([Na]s) is directly proportional to the ratio of total-body exchangeable sodium ([Na]e) plus total-body exchangeable potassium ([K]e) relative to TBW by the formula: [Na]s = 1.11([Na]e + [K]e)/TBW − 25.6, the so-called Edelman equation (Fig 1).18 Another group subsequently confirmed this concept, although with a different slope (0.487) and intercept (+71.54).19 Approximately 20% to 30% of total-body sodium is nonexchangeable,20 residing in bone, and ~55% of total-bone sodium is nonexchangeable.21

However, a significant percentage of exchangeable sodium and potassium (herein referred to as cations) is not osmotically active (although still exchangeable), being sequestered within cells (eg, muscle) or bound extracellularly, that is, “third-spaced.”22-23 In animal models, osmotically inactive sodium storage occurs in skin bound to glycosaminoglycans.24-26 Mobilization of this sodium may occur through stimulation of macrophage tonicity enhancer-binding protein.27 This transcription factor induces macrophage synthesis of VEGF-C (vascular endothelial growth factor C), which stimulates lymphatic capillary synthesis and mobilization of bound sodium.

In humans, such osmotically inactive sodium in skin and muscle can be noninvasively assessed using magnetic resonance imaging, and its mobilization can be demonstrated. Levels of skin sodium increase with age and are variable from patient to patient.28-29 Edelman ascribed in large measure the negative intercept (−25.6) of his equation to exchangeable but osmotically inactive cations.18 However, the concept of “osmotically inactive” sodium has been questioned.20

The fraction of exchangeable cations that are osmotically inactive has been estimated to range from one-quarter30 to more than half.31 Importantly, the proportion of exchangeable cations that are osmotically active may be dynamic, which can result in alterations in serum sodium levels not explainable by mass external balance of sodium, potassium, and water. However, in some animal studies, mass balance explained observed changes.32-33 Additionally, other intracellular effective organic molecules, termed osmolytes, help maintain cell volume and contribute to total-body tonicity.20 They can be gained or lost along with water to regulate cell volume, with resulting reciprocal changes in serum sodium levels, an effect that would
result in inaccurate prediction of the change in serum sodium level based solely on mass balance of cations and water.20

Hence, serum sodium concentration can decrease if the external mass balance of exchangeable cations and water alters their ratio, the osmotically inactive fraction of cations increases, loss of intracellular organic osmolytes occurs, or some combination exists. Furthermore, disordered external balance may result from net gain of water, net loss of cations, or both. The former is termed dilutional hyponatremia, and the latter, depletional. In the case of TAH, evidence exists for excessive fluid intake, water retention from impaired excretion, cation depletion, and osmotic inactivation of cations, with different mechanisms demonstrable in different patients, which may explain the marked variability in the clinical presentation of TAH, for example, in the duration of thiazide exposure.

### Excessive Water Intake

Hyponatremia requires intake of water to develop. Occasionally, TAH has been reported in patients with primary polydipsia,14,35 but the usual presentation involves more modest fluid intake. Two studies acutely rechallenged patients with a history of TAH and found relative polydipsia with weight gain.16,37 Friedman et al16 administered a single dose of hydrochlorothiazide plus amiloride to 11 patients with a history of TAH compared with 10 healthy volunteers and 11 patients previously treated with thiazides without TAH. In patients with TAH, serum sodium levels decreased by 5.5 mEq/L within 6 to 8 hours compared with 1.2 and 1.8 mEq/L in control groups. All patients with TAH gained weight, while both control groups lost weight, with no difference in sodium and potassium excretion, free-water clearance, or ADH levels.

Similarly, Frenkel et al37 administered a single dose of hydrochlorothiazide to 15 patients with a history of TAH compared with 15 patients receiving thiazides without a history of TAH. Plasma sodium levels significantly decreased in patients with TAH compared with controls, along with greater fluid intake compared with controls and a tendency for weight gain versus weight loss in controls. Together these studies suggest an important primary role for increased fluid intake in addition to impaired free-water excretion in cases of TAH developing rapidly following re-exposure.

### Impaired Free-Water Excretion

Thiazides impair free-water excretion by multiple potential mechanisms (Box 2). The appropriate physiologic response to hypotonic hyponatremia is ADH suppression, urine dilution, and excretion of the excess water. Additionally, the ability to normally excrete free water depends on adequate distal delivery of fluid to dilute along with a reasonable solute load to excrete. Distal delivery is hampered in kidney failure by reduced GFR and in states of reduced effective circulating volume due to both reduced GFR and enhanced proximal tubule reabsorption of filtrate.38,39 In most reported cases of TAH, urine osmolarity is inappropriately concentrated, that is, >100 mOsm/L. This may occur by several mechanisms and is incompletely understood. Furthermore, even patients with a history of TAH who are currently normonatremic may have impaired urinary dilution following a water load in the absence of a thiazide, suggesting that in these patients, thiazide use may have unmasked an underlying defect in dilution.14,40 Additionally, at least 2 studies found decreased urea excretion in patients with TAH compared with nonhyponatremic thiazide users, suggesting reduced solute load limiting maximal free-water excretion.37,41

The osmolarity of fluid entering the distal convoluted tubule is somewhere between 100 and 150 mOsm/L (Fig 2). Further NCC-mediated sodium reabsorption in the distal convoluted tubule results in maximally dilute urine (~ 50 mOsm/L). The direct effect of thiazides to inhibit NCC impairs maximal dilution, which prevents reduction of urine osmolarity from 100 to 150 mOsm/L to 50 mOsm/L. With usual solute intake of 500 to 1,000 mOsm/d, 3 to 6 L of urine would be produced with

![Diagram of total-body sodium compartments](image-url)
urine osmolarity of 150 mOsm/L. This degree of impaired dilution would not result in hyponatremia with usual intake of water, but can with excessive intake.34,35 Furthermore, if the sole pathophysiologic mechanism for TAH were NCC inhibition, urine osmolarity would be no greater than 150 mOsm/L. The vast majority of cases have significantly higher urine osmolarity with the average urine osmolarity of ~400 in the meta-analysis cited,11 indicating that additional mechanisms than just NCC inhibition are involved.

The effect of thiazide-induced inhibition of NCC per se on free-water excretion is demonstrable during a water diuresis or with diabetes insipidus. Early et al36 showed that dogs undergoing water diuresis had urine osmolarities ranging from 30 to 32 mOsm/L that increased to 85 to 110 mOsm/L following chlorothiazide infusion.

Similarly, Earley and Orloff37 studied 4 patients with nephrogenic diabetes insipidus and showed that baseline urine osmolarities <100 mOsm/L increased following hydrochlorothiazide to >100 mOsm/L, with reductions in urine volume often >50%. Interestingly, when the thiazide treatment was discontinued, urine osmolarity remained elevated and urine output reduced as long as sodium intake was low (9 mEq/d), probably maintained by markedly reduced distal delivery of filtrate and ADH-independent residual water permeability (RWP).39 A marked reduction in distal delivery of filtrate following acute thiazide exposure was demonstrated by micropuncture in ADH-deficient Brattleboro rats.40 However, in animals exposed long term to hydrochlorothiazide, distal delivery was only modestly reduced. In the long-term steady state in patients, when balance is achieved, urinary solute would approximate solute intake, and doubling of urine osmolarity should halve urine output.

Thiazide-induced mild volume depletion reduces the ability to excrete free water by reducing delivery of filtrate39 (GFR decrease34,35 plus enhanced proximal tubular reabsorption43,44) and possibly by hemodynamically stimulating ADH release. The overwhelming majority of reported cases of TAH had urine osmolarity >200 mOsm/L and usually >300 mOsm/L, proving that simple inhibition of NCC is not the sole mechanism impairing urinary dilution. Increased collecting duct permeability to water must also be present, suggesting ADH release.

However, ADH measurement in patients with TAH has produced conflicting results. Some studies found elevated levels,46-48 while others did not.16,37,41 Chronic hyponatremia itself may result in reversible alterations of osmoreceptor function, including a lower threshold for ADH release. Wall et al49 performed a hypertonic saline solution infusion in a hyponatremic patient and repeated this when normonatremic. The osmotic threshold for ADH release was 12 to 13 mOsm/L lower while hyponatremic.49 This phenomenon, if present during TAH, could explain the delayed resolution of hyponatremia that often takes days, long after the inhibition of NCC has worn off and any volume deficit has been restored.50,51 In contrast, rats made hyponatremic and then challenged with hypertonic saline solution infusions did not show alterations in the osmotic threshold for ADH release.52

Animal data support an ADH-independent mechanism of thiazides to increase collecting duct water permeability. Cesar and Magaldi13 performed in vitro microperfusion of inner medullary collecting ducts of ADH-deficient Brattleboro rats and showed that thiazide exposure in the perfusate enhanced osmotic water permeability, an effect
that was abrogated by adding PGE2 (prostaglandin E₂) to
the solution to simulate basolateral exposure.⁵³

Also studying Brattleboro rats, Shirley et al.⁵⁴ demonstrated significant increases in papillary interstitial sodium (from 165 to 212 mmol/L), calculated urea (from 79 to 224 mmol/L), and osmolarity (from 451 to 692 mOsm/L) following thiazide exposure, which would enhance water reabsorption through residual water permeability.¹⁹ Sodium depletion in Brattleboro rats resulted in doubling of urine osmolarity with frank development of hyponatremia in the absence of ADH.⁵⁵ In experimental animals with lithium-induced nephrogenic diabetes insipidus, aquaporin 2 expression is reduced by ~80%, which is partially reversed by hydrochlorothiazide.⁵⁶ an effect confirmed by semiquantitative immunoblotting and immunohistochemistry and resulting in a near tripling of urine osmolarity with urine output down by two-thirds.

In a genome-wide association study of 157 patients with TAH, ~50% (vs ~25% of controls) harbored at least 1 copy of a variant allele of the prostaglandin transporter SLCO2A1 with reduced ability to transport PGE₂ across the apical cell membrane (Fig 3A and B). Failure of this transporter reduces activation of the PGE₂ receptor subtypes EP₁ and EP₃ on the basolateral side, which otherwise would antagonize the effect of ADH by causing retrieval of aquaporin 2 channels from the luminal membrane (Fig 3A, the normal circumstance),⁵⁷ supported by basolateral PGE₂ perfusion in the microperfusion study outlined above.⁵³

In contrast, increased luminal PGE₂ activates apical EP₄ prostaglandin receptors, which have the opposite effect to EP₁ and EP₃ activation and mediate aquaporin 2 transfer to the apical membrane in the absence of ADH (Fig 3B, the situation with a variant allele). Thiazide use has been associated with greater urinary excretion of PGE₂ and its metabolite in TAH cases, although the reason for this is uncertain. Of note, in the genome-wide association study, 25% of controls harbored the variant allele without apparent susceptibility to TAH.

**Solute Depletion**

That cation depletion could accompany TAH makes intuitive sense given the natriuretic and kaliuretic effects of thiazides. After 3 days of 100 mg of hydrochlorothiazide in healthy volunteers, weight decreased by 2 kg despite reductions in serum sodium levels by 4 to 5 mEq/L,⁴⁰ suggesting significant cation depletion. When thiazides are given for 3 months or longer, some studies showed persistent weight loss⁵⁸,⁵⁹ while another did not.⁶⁰ Furthermore, following cessation of treatment, weight gain occurred.⁶¹

In earlier studies in hypertensive patients given thiazides, one study showed reduction of total-body exchangeable sodium⁵⁸ while others did not.⁵⁸,⁵⁹ Studying patients specifically with TAH, Fichman et al.⁴⁶ found a negligible decrease in exchangeable sodium but a 25% decrease in exchangeable potassium, with no change in TBW. Increasing potassium intake improved the hyponatremia.

Musch and Decaux.⁶² recently studied 14 patients with TAH, of whom 5 had serum uric acid level < 4 mg/dL and fractional excretion of uric acid (FEUA > 12%, suggesting SIADH. All patients were treated with 2 L of normal saline solution per 24 hours and potassium as needed. Ten patients had balance studies showing 600 mEq of retained sodium and potassium, values similar to retained cations in 6 patients with hyponatremia and volume depletion from gastrointestinal losses (641 mEq of retained cations). These data indicate that at least some patients with clinically euvoletic TAH and laboratory values consistent with SIADH

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**Figure 3.** (A) Role of SLCO2A1 in thiazide-associated hyponatremia (TAH). Under normal conditions, luminal prostaglandin E₂ (PGE₂) is transported through the prostaglandin transporter PGT to the basolateral side, leading to activation of PGE₂ receptor subtypes 1 (EP₁) and EP₃. This causes retrieval of aquaporin 2 (AQP2) receptors from the luminal membrane, antagonizing the hydro-osmotic effect of antidiuretic hormone (ADH), enhancing free-water excretion. (B) In patients with reduced PGT activity, increased luminal PGE₂ instead activates luminal EP₄ receptors, causing insertion of AQP2 in the absence of ADH, directly reducing urine dilution and free-water excretion.
may have significant underlying cation deficiency and not primary water retention.

### Osmotic Inactivation of Cations

To demonstrate the dynamic activation/inactivation of cations requires careful metabolic balance studies of sodium, potassium, and water. Circumstantial evidence for a dynamic nature exists. Heer et al.\(^6\)\(^3\) showed that increasing sodium intake from normal levels to very high levels during a 3-week period resulted in cumulative sodium retention of 1,700 mEq with no change in body weight or serum sodium levels. In a study of more than 2,000 athletes engaged in long-distance events, >80% maintained a normal serum sodium level despite a range of body weight changes from −12% to +6%, suggesting osmotic inactivation in those maintaining a normal serum sodium level despite losing weight from hypotonic fluid loss and osmotic activation in those gaining weight from hypotonic fluid ingestion without a decrease in serum sodium level.\(^1\)^\(^4\)

Osmotic inactivation may be a contributing mechanism in TAH. Fuisz et al.\(^1\)^\(^3\) performed balance studies upon thiazide rechallenge in a woman with TAH. Serum sodium level decreased by 13 mEq/L over 24 hours with measured loss of 143 mEq of sodium and 750 mL of water, indicating either osmotic inactivation or inordinate potassium losses. In a second rechallenge after sodium loading, serum sodium level decreased 9 mEq/L despite measured gains of 135 mEq of sodium and 710 mL of water. Potassium balance data were not provided.\(^1\)^\(^4\)

Johnson and Wright\(^1\)^\(^5\) rechallenged a patient with TAH and found a 13 mEq decrease in serum sodium level over 18 hours despite net urinary losses of only 55 mEq of cations (sodium and potassium) and 193 mL of water.

Using isotope-dilution studies in a series of patients with TAH, Fichman et al.\(^4\)^\(^6\) found essentially normal total-body exchangeable sodium and TBW, but a marked deficit of total-body exchangeable potassium. The osmotically inactive percentage of exchangeable sodium and potassium was not defined, but the ratio of extracellular sodium to exchangeable sodium was reduced, suggesting intracellular movement of sodium or osmotic inactivation. Other studies in both experimental animals\(^6\)^\(^5\)\(^,\)\(^6\)\(^,\)\(^6\)\(^,\)\(^6\) and humans\(^6\)^\(^6\)\(^,\)\(^6\) also demonstrate thiazide-induced increases in cellular sodium content involving red blood cells\(^6\)^\(^5\)\(^,\)\(^6\)\(^,\)\(^6\) and muscle.\(^6\)^\(^7\) Careful balance studies are required to more properly define the role of osmotic inactivation in TAH. It still is uncertain to what extent loss of intracellular organic osmolytes explains discrepant external balance studies, as opposed to osmotic inactivation.\(^2\)^\(^0\)

### Differential Diagnosis

The main diagnostic question when facing a euvoletic patient with TAH is differentiation from SIADH. That would ultimately be determined by complete correction of the hyponatremia following discontinuation with no recurrence as long as the thiazide treatment is not restarted.

In some cases of TAH, recovery may be quick following cessation of the diuretic therapy and administration of saline solution. More commonly, cases may take days to weeks to recover, although subtle defects in free-water excretion may underlie some of these cases.\(^4\)^\(^0\)^\(^,\)\(^5\)^\(^1\)

In euvoletic patients with hyponatremia suspected of having SIADH, subclinical volume depletion is possible and physical examination is neither sensitive nor specific enough to reliably make this distinction.\(^6\)^\(^8\)^\(^,\)\(^6\)^\(^9\) Laboratory tests used in this differential include creatinine, serum urea nitrogen, serum uric acid, urine sodium, fractional excretion of sodium, fractional excretion of urea, and fractional excretion of uric acid (FEUA).\(^7\)^\(^0\) In volume depletion, serum levels are higher and fractional excretions are lower compared with SIADH, although there is significant overlap,\(^7\)^\(^0\) with cutoffs proposed (Table 1). The ultimate test is the response to saline solution challenge, with complete correction indicating subclinical volume depletion, although partial response may be seen with SIADH when urinary cation concentration is lower than serum sodium levels.\(^7\)^\(^1\) If the urinary cation concentration increases to levels higher than serum sodium, the response to saline solution is likely to be worsening of the hyponatremia, termed desalination.\(^7\)^\(^2\)

Typically, patients with TAH have laboratory values consistent with SIADH, even including low serum uric acid and high FEUA despite the tendency of thiazides to increase serum uric acid levels. Fenske et al.\(^7\)^\(^3\) compared patients using a diuretic with SIADH diagnosed with hyponatremic patients without SIADH (hemodynamic ADH) also using a diuretic and found FEUA to be the only significant discriminator (area under the curve, 0.96); at values >12%, sensitivity was 86% for SIADH with specificity of 100%.

In contrast, Sonnenblick and Rosin\(^7\)^\(^4\) reported a mean FEUA of 28% in 7 patients with TAH (no underlying

### Table 1. Laboratory Values to Differentiate Subtle Volume Depletion From SIADH

<table>
<thead>
<tr>
<th>Test</th>
<th>Volume Depletion</th>
<th>SIADH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine [Na], mEq/L</td>
<td>&lt;30</td>
<td>&gt;30 (unless minimal intake)</td>
</tr>
<tr>
<td>FE(_{\text{Na}})</td>
<td>&lt;0.5%</td>
<td>&gt;0.5%</td>
</tr>
<tr>
<td>&lt;0.15% if urine/plasma creatinine ratio &gt; 140</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FE(_{\text{urea}})</td>
<td>&lt;55%</td>
<td>&gt;55%</td>
</tr>
<tr>
<td>&lt;45% if urine/plasma creatinine ratio &gt; 140</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum uric acid, mg/dL</td>
<td>&gt;4</td>
<td>&lt;4</td>
</tr>
<tr>
<td>FE(_{\text{UA}})</td>
<td>&lt;12%</td>
<td>&gt;12% (while hyponatremic)</td>
</tr>
</tbody>
</table>

Note: Values supporting volume depletion suggest thiazide-induced hyponatremia but do not rule out underlying SIADH, which can only be determined after restoration of volume. Values typical of SIADH can also be found in thiazide-induced hyponatremia.

Abbreviations: FE\(_{\text{Na}}\), fractional excretion of sodium; FE\(_{\text{UA}}\), fractional excretion of uric acid; FE\(_{\text{urea}}\), fractional excretion of urea; [Na], sodium concentration; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

Based on information in Decaux and Musch.\(^7\)^\(^2\)
SIADH) that decreased to normal (mean, 9.8%) with resolution of the hyponatremia. Furthermore, as noted, cases of TAH resembling SIADH may have significant cation depletion with elevated FE\textit{U}_\text{A} that may not normalize with correction of the hyponatremia.\textsuperscript{75,76} Musch and Decaux\textsuperscript{62} studied 6 patients with thiazide-induced hyponatremia and serum uric acid levels < 4 mg/dL (suggesting SIADH) and found elevated FE\textit{U}_\text{A} (range, 14%-38%) that increased in 2 patients following treatment with isotonic saline solution and potassium (22% and 44%) despite correction of the hyponatremia. Hence, it may not be possible by any laboratory test to determine with certainty on presentation whether a euvoletic hyponatremic patient using a thiazide has TAH or underlying SIADH.

**Therapy**

The mainstay of therapy of TAH is immediate cessation of thiazide use. In the report from the Hyponatremia Registry, continuation of the thiazide treatment was associated with reduced rates of improvement irrespective of additional therapy.\textsuperscript{10} Any associated sodium depletion should be corrected based on the physical examination and basic laboratory values outlined (Table 1).\textsuperscript{70} The imprecision of both physical examination and laboratory values for assessing true sodium deficits precludes a standard recommendation applicable to all patients. Any potassium deficiency should be corrected. Free-water intake should be restricted. The major risk of acute (<48 hours duration), severe (<125 mEq/L), and symptomatic hyponatremia is cerebral herniation. Both American and European guidelines have addressed the use of 3% saline solution in such situations, and the reader is referred to these publications for specific recommendations.\textsuperscript{25,77} The major risk of chronic (>48 hours’ duration) and severe hyponatremia is osmotic demyelination syndrome resulting from overly rapid correction. All such chronic cases should be watched closely for brisk water diuresis heralded by increasing urine volume and decreasing urine osmolality.\textsuperscript{77} This is most likely to occur in cases of TAH mediated by volume depletion and hemodynamic ADH release ameliorated by aggressive saline solution administration. A reasonable rule of thumb to suggest the possibility of overly rapid correction is urine output > 1 mL/kg/h.\textsuperscript{77} A detailed discussion of hypertonic saline solution regimens, the use of desmopressin, and appropriate correction rates in chronic hyponatremia is beyond the scope of this article and can also be found in the mentioned guidelines.\textsuperscript{25,76}

**Conclusion**

Hyponatremia can complicate thiazide use in a minority of susceptible patients and can result in significant morbidity and even mortality. Risk factors include older age and female sex, with low body mass also possibly contributing. A genetic susceptibility has recently been uncovered involving a polymorphism in the apical prostaglandin transporter of the distal nephron. Although frequently developing early after thiazide treatment initiation, many cases present after months or years of use. Many cases are asymptomatic or have mild symptoms, but seizures and/or coma may develop, especially in those with acute onset.

The pathophysiology is incompletely understood and includes some combination of excessive fluid intake, cation depletion, osmotic inactivation of sodium, and reduced ability to maximally excrete free water due to multiple possible mechanisms. These include reduced distal delivery of filtrate, reduced solute load (urea), inhibition of NCC, and increased (compared to residual water permeability) collecting duct permeability to water mediated by ADH in some cases, prostaglandins in some cases, and perhaps by thiazides themselves. The predominant pathophysiologic mechanism(s) varies from patient to patient. The cornerstone of therapy is cessation of thiazide treatment, cation repletion, and oral fluid restriction. If severely symptomatic, 3% saline solution may be indicated. Overly rapid correction must be avoided in all cases.

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