CLINICAL RESEARCH STUDY

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Risk of Electrolyte Disorders, Syncope, and Falls in Patients Taking Thiazide Diuretics: Results of a Cross-Sectional Study

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ABSTRACT

BACKGROUND: Thiazide diuretics are a mainstay in the management of hypertension and often associated with dyselectrolytemias. We investigated the prevalence of and risk factors for hyponatremia and hypokalemia in thiazide users, substance-specific differences, and the association of thiazides with syncope and falls.

METHODS: In this cross-sectional analysis all patients admitted to an interdisciplinary emergency department in Switzerland between January 1, 2017, and December 31, 2018, with measurements of serum sodium and potassium were included. Data regarding serum electrolytes and creatinine were analyzed to classify for dysnatremias, dyskalemias, and acute kidney injury. Chart reviews were performed to screen for syncope or falls.

RESULTS: A total of 1604 patients (7.9%) took thiazides. Acute kidney injury was significantly more common in thiazide users (22.1 vs 7%, $P < .0001$). Hyponatremia (22.1 vs 9.8%, $P < .0001$) and hypokalemia (19 vs 11%, $P < .0001$) were more frequent with thiazides. Thiazide use together with higher age and female sex were independent predictors of hyponatremia and hypokalemia. A dose-dependent effect was found for electrolyte disorders, and there was a variance in risk between the investigated substances with chlorthalidone bearing the highest and hydrochlorothiazide the lowest risk. Patients taking thiazide diuretics had significantly more episodes of syncope and falls.

CONCLUSIONS: Thiazide use is a clear risk factor for hyponatremia and hypokalemia. The effect appears to be dose-dependent and highly variable depending on the substance. Syncope and falls seem to be causally related to thiazide use. Especially in patients who are elderly, female, and prone to falls, the use of thiazide diuretics should be thoroughly questioned.

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BACKGROUND

Thiazide diuretics are commonly prescribed drugs and are considered a mainstay in the treatment of arterial hypertension.[1,2] Thiazides or thiazide-like diuretics such as hydrochlorothiazide, indapamide, chlorthalidone, and metolazone were found to be associated with hyponatremia and hypokalemia.[1,3] Moreover, thiazides were described to be independently associated with hypomagnesemia.[4] The occurrence of thiazide-associated hyponatremia especially has been in the focus of research in recent years.[1,5,6] Nevertheless, the mechanisms leading to hyponatremia through thiazide diuretics appear to be complex and are incompletely understood so far:[1] First, increased intake of free water was shown to be present in patients with a history of thiazide-associated hyponatremia compared with controls taking thiazides that did not develop hyponatremia.[7,8] Second, the ability of the kidney to adequately excrete electrolyte-free water is impaired by reduced distal delivery of filtrate, a direct inhibition of the sodium-chloride cotransporter in the distal tubule by the drug, and a reduced solute load (urea) causing a reduction in the maximum capacity to excrete free water.[1] Third, sodium and potassium loss is apparent through the natriuretic effect of thiazide diuretics.[9,10]

CLINICAL SIGNIFICANCE

- Hyponatremia (22%) and hypokalemia (19%) were common in patients taking thiazide diuretics.
- A thiazide diuretic was an independent predictor of hyponatremia and hypokalemia with specific substance and dose-dependent effects, with chlorthalidone showing the highest and hydrochlorothiazide the lowest risk.
- Thiazides and increasing age were independent risk factors for syncope and falls.
- A more careful approach to prescribing thiazide diuretics in elderly patients is recommended.

Given the mentioned mechanisms of action, it is not surprising that thiazide use is associated with electrolyte disorders. In a large systematic review, it was described that thiazide use was independently associated with the occurrence of hyponatremia and that female gender and advanced age are independent predictors of its occurrence.[6] Hypokalemia and its association with thiazide use on the other hand is less well-studied. Furthermore, evidence concerning comedications, which may influence occurrence of electrolyte disorders during thiazide therapy, is scarce. Because thiazide diuretic use is commonly associated with discrete volume depletion as well as hyponatremia, an association with orthostatic syncope and falls may be assumed. Hence, we aimed to investigate 1) the prevalence of and risk factors for hyponatremia and hypokalemia in patients taking thiazide diuretics; 2) substance-specific risks for the electrolyte disorders; and 3) whether thiazide use is associated with an increased risk for syncope and falls.

METHODS

Study Design and Setting

To investigate the prevalence and risk factors of electrolyte disorders in patients taking thiazide diuretics as well as their association with syncope and falls, a cross-sectional analysis of all patients admitted to the emergency department (ED) of the Buergerspital Solothurn between January 1, 2017, and December 31, 2018, with on-admission measurements of sodium and potassium was conducted. The Department of Emergency Medicine is an interdisciplinary ED with approximately 35,000 consultations per year including medical, surgical, and trauma patients.

All patients age 18 years and older admitted to the ED during the study period with measurements of sodium and potassium on admission, who did not withdraw consent to scientific use of their data verbally or written, were included.

Data on age, sex, length of hospital stay, in-hospital mortality, medical history, and regular medication was collected. Furthermore, laboratory results such as serum sodium, potassium, and serum creatinine were gathered. Electrolyte disorders were classified as hyponatremia (serum sodium <135 mmol/L), hypernatremia (sodium >145 mmol/L), hypokalemia (serum potassium <3.5 mmol/L), and hyperkalemia (potassium >5.0 mmol/L). Detailed chart reviews were performed for all patients with thiazide diuretics on admission by the same 2 persons (SR, SB). In addition, all patients were screened for presence of syncope and falls on ED admission. The list of diagnoses as well as the history of the emergency medical report were screened for presence of falls or syncope on admission. Daily thiazide medication and type of thiazide diuretic as well as daily doses were extracted from the patients' electronic charts. In patients taking thiazide diuretics irregularly, the mean daily dose was calculated, whereas thiazide diuretics taken on an as-needed basis were not included in the analysis. Equivalent doses of thiazides were assumed on basis of the available literature:[11] Hydrochlorothiazide 25 mg equivalent to chlorthalidone 12.5 mg, metolazone 5 mg, or indapamide 2.5 mg. Acute kidney injury was defined according to the Acute Kidney Injury Network (AKIN) definition.[12]

Statistical Methods

After completion of data collection, data were cleaned and outliers (>95% confidence interval) were reconfirmed or corrected. Data were exported to a statistical software package (SPSS for Windows, version 23; SPSS Inc or STATA IC 15.1, STATA CORP, LCC) for analysis. Continuous data are presented as median and first to third quartiles or as mean and standard deviation (± SD). Distribution of continuous variables was assessed using normal plots and

logarithm transformation was performed when appropriate. Categorical data are presented as absolute counts and percentages. Between-group comparisons of continuous variables were performed using the Mann-Whitney U test. Categorical variables were compared using the $\chi 2$ test or Fisher exact test. Logistic regression was used to explore risk factors with presence of hyponatremia and hypokalemia. Robust standard errors with patient identification as the cluster variable were used. A 2-sided P value <.05 was considered statistically significant.

Ethical Considerations

The study was approved by the ethics committee, Ethikkommision Nordwest-und Zentralschweiz (2020-01319). There was no patient and public involvement in the present study.

RESULTS

In the investigated time period from January 1, 2017, through December 31, 2018, a total of 64,713 consultations (2017: 31,311; 2018: 33,402) were registered in the Department of Emergency Medicine of the Buergerspital Solothurn. Measurements of serum sodium and potassium were available for 20,421 consultations of patients. Mean age of patients in the investigated collective was 59 years (SD 22) and 50.7% were female. Mean length of hospital stay was 3.8 days (SD 5.0) and in-hospital mortality was 1.6%. Table 1 gives baseline characteristics of the study population.

Characteristics of Patients on Thiazide Diuretics

A total of 1604 patients (7.9%) were taking thiazide diuretics on a daily basis. Mean age of patients with thiazide medication was 74 years (SD 13) and 51.5% were female; 9.7% of patients on thiazide diuretics had chronic kidney disease compared with 3.4% of patients without thiazides ($P < .0001$). Mean creatinine on admission was 112 μmol/L (SD 45.6) in patients on thiazide diuretics, whereas 83 μmol/L (88.3) in patients without thiazide medication ($P < .0001$). Acute kidney injury was more common in patients on thiazide diuretics, occurring in 21.4% of admissions, compared with 7.2% in patients without thiazides ($P < .0001$). Mean length of hospital stay was longer in patients on thiazide diuretics (5.5. days [SD 6.0] vs 3.6 days [SD 4.8], $P < .0001$). A total of 129 patients on thiazide diuretics (8.0%) needed intensive or intermediate care treatment. Of the patients taking thiazide diuretics, 3.1% died, and 1.5% of patients without thiazide diuretic medication died during hospitalization ($P < .0001$). Table 2 gives a comparison between patients with and without thiazide medication.

Table 1 Baseline Characteristics

	All patients
Age (years)	59 (SD 22)
Sex (female)	50.7%
LOS (days)	3.8 (SD 5.0)
Mortality	1.6%
CKD	3.9%
AKI	8.3%
Creatinine actual (umol/L)	85.0 (50.9)
NSAID	12.6%
Loop diuretics	9.6%
ACE inhibitors	12.3%
AT2-R-blockers	14.2%
Renin inhibitors	0.2%

ACE = angiotensin-converting enzyme; AKI = acute kidney injury; AT2-R = Angiotensin-2-receptor; CKD = chronic kidney disease; LOS = length of stay; NSAID = non-steroidal anti-inflammatory drugs; SD = standard deviation.

Table 2 Baseline Characteristics

	No Thiazides	Thiazide	*P* Value
Age (years)	57 (SD 22)	74 (SD 13)	<.0001
Sex (female)	50.6%	51.7%	.42
LOS (days)	3.6 (SD 4.8)	5.5 (SD 6.0)	<.0001
Mortality	1.5%	3.1%	<.0001
CKD	3.4%	9.7%	<.0001
AKI	7.2%	21.4%	<.0001
Creatinine actual (μmol/L)	82.7 (SD 45.6)	111.7 (88.3)	<.0001
NSAID	12.5%	14.4%	.027
Loop diuretics	8.6%	21.2%	<.0001
ACE inhibitors	10.4%	34%	<.0001
AT2-R-blockers	11.3%	48%	<.0001
Renin inhibitors	0.1%	0.9%	<.0001

ACE = angiotensin-converting enzyme; AKI = acute kidney injury; AT2-R = Angiotensin-2-receptor; CKD = chronic kidney disease; LOS = length of stay; NSAID = non-steroidal anti-inflammatory drugs; SD = standard deviation.

Thiazide Type, Dose, and Comedication

A total of 1346 patients (84% of patients with thiazides) were taking hydrochlorothiazide with a mean daily dose of 16.2 mg (SD 9.6), 26 (1.6%) were taking chlorthalidone with a mean daily dose of 17.1 mg (SD 6.5), 88 (5.5%) were taking indapamide with a mean daily dose of 1.8 mg (SD 0.9), and 152 (9.5%) were taking metolazone with a mean daily dose of 5.1 mg (SD 2.7). A total of 342 patients (21.3%) had a daily combination of loop and thiazide diuretic, and 561 (35%) were taking a combination of thiazide diuretic and angiotensin-converting enzyme inhibitor (ACE-I), 770 (48%) a combination with an angiotensin-2-receptor-blocker (ARB), and 14 (0.01%) a combination with a renin-inhibitor.

Thiazide Diuretics and Electrolyte Disorders

In patients on thiazide diuretics, mean serum sodium was 137 mmol/L (SD 5) compared with 138 mmol/L (SD 3) in

Table 3 Electrolytes in Patients with and without Thiazide Diuretics.

	No Thiazides	Thiazide	*P* Value
Serum Sodium (mmol/L)	138 (SD 3)	137 (SD 5)	<.0001
Hyponatremia	9.8%	22.1%	<.0001
Hypernatremia	0.6%	0.4%	<.0001
Serum potassium (mmol/L)	3.94 (SD 0.5)	3.91 (SD 0.6)	.008
Hypokalemia	11%	19%	<.0001
Hyperkalemia	1.8%	3.8%	<.0001

SD = standard deviation.

patients without thiazide diuretics ($P < .0001$). A total of 354 patients (22.1%) had hyponatremia compared with 9.8% in the patient group without thiazide medication ($P < .0001$). Hypernatremia was significantly less common in patients on thiazide diuretics (0.4% vs 0.6%, $P < .0001$).

Serum potassium concentration was in absolute numbers comparable between groups being 3.94 mmol/L (SD 0.5) in patients without thiazides compared with 3.91 mmol/L (SD 0.6; $P = .008$). Hypokalemia was significantly more common in patients on thiazide diuretics (19% vs 11%, $P < .0001$). Hyperkalemia was also more prevalent in patients on thiazide (3.8%) compared with those without thiazide medication (1.8%) ($P < .0001$). Table 3 summarizes the findings on electrolyte disorders in the patient collective.

In the multivariable logistic regression analysis, age (odds ratio [OR] 1.03, 95% confidence interval [CI]: 1.029-1.035, $P < .0001$) proved to be an independent risk factor for the development of hyponatremia, whereas male sex proved to be protective (OR 0.76, 95% CI: 0.67-0.84, $P < .0001$). Thiazide diuretics were found to be the strongest independent predictor for hyponatremia in the investigated patient collective (OR 1.55, 95% CI: 1.33-1.80, $P < .0001$). Among thiazide diuretics, chlorthalidone had the strongest association with the presence of hyponatremia (OR 7.63, 95% CI: 3.46-16.84, $P < .0001$), followed by metolazone (OR 4.93, 95% CI: 3.50-6.94), $P < .0001$), indapamide (OR 3.49, 95% CI: 2.09-5.81, $P < .0001$), and hydrochlorothiazide (OR 2.28, 95% CI: 1.97-2.65, $P < .0001$). Figure 1 shows the association of the various types of thiazide diuretics and the risk for hyponatremia.

Comparing the equivalent dose of the different thiazide diuretics, a higher equivalent dose was significantly associated with an increased risk of developing hyponatremia (OR 1.01, 95% CI: 1.00,1.02, $P = .008$). In addition, ACE-I (OR 1.19, 95% CI: 1.03-1.38, $P = .016$) as well as ARB (OR 1.20, 95% CI: 1.05-1.38, $P = .008$) were identified as risk factors for hyponatremia.

In terms of developing hypokalemia, male sex proved to be protective (OR 0.61, 95% CI: 0.55,0.68, $P < .0001$) in the investigated patient collective. Age was also slightly protective for the presence of hypokalemia (OR 0.99, 95% CI: 0.993,0.997, $P < .0001$). Among the analyzed daily

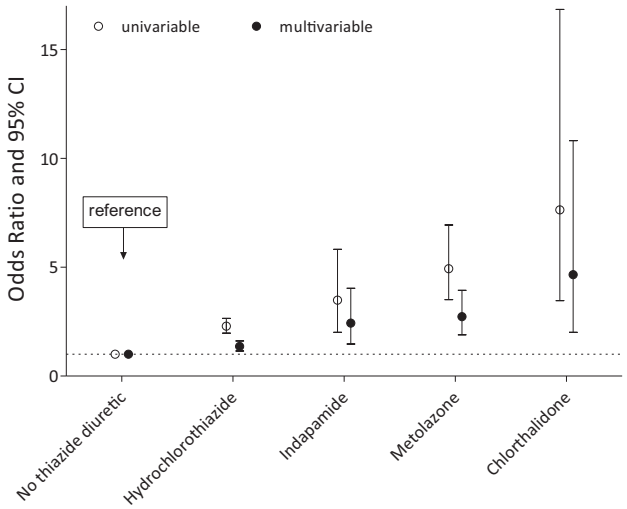

Figure 1 Types of thiazide diuretics and their association with presence of hyponatremia.

medication, thiazide diuretics were the strongest risk factors for hypokalemia (OR 2.45, 95% CI: 2.07-2.89, $P < .0001$), closely followed by loop diuretics (OR 1.46, 95% CI: 1.22-1.75, $P < .0001$). All thiazide diuretics were significantly associated with hypokalemia on ED admission with chlorthalidone bearing the highest risk for hypokalemia (OR 22.7, 95% CI: 9.26-55.79, $P < .0001$) followed by indapamide (OR 4.7, 95% CI: 2.99,7.54, $P < .0001$), metolazone (OR 2.6, 95% CI: 1.63-4.15, $P < .0001$), and hydrochlorothiazide (OR 2.23, 95% CI: 1.89-2.62, $P < .0001$). Figure 2 gives the risks of the various thiazide diuretics for hypokalemia. Similar to the results in hyponatremia, a higher thiazide equivalent dose was significantly associated with prevalence of hypokalemia (OR 1.01, 95% CI: 1.00-1.02, $P = .007$).

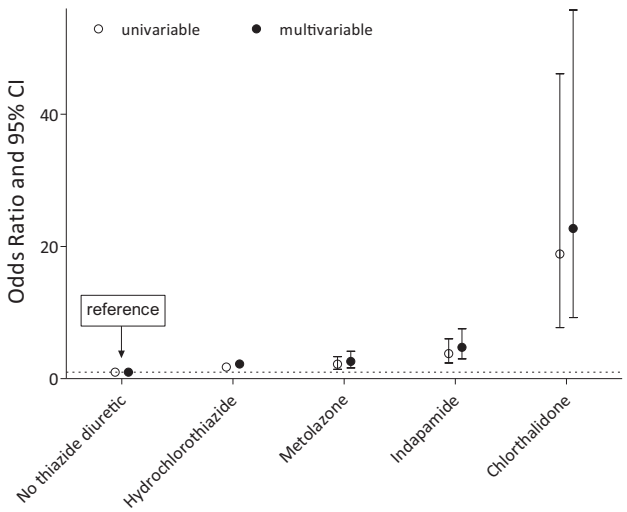

Figure 2 Types of thiazide diuretics and their association with presence of hypokalemia.

Falls and Syncope in Patients on Thiazide Diuretics

Overall, 8.1% of all patients admitted to the ED presented with a recent fall and 3.3% with a syncope, respectively. Patients with thiazide diuretic medication presented to the ED more frequently with a recent fall (20.5%) compared with patients without thiazide diuretic (7.0%; $P < .0001$). Additionally, episodes of syncope were significantly more common in patients on thiazide diuretics (6.2%) compared with patients without thiazides (3.1%; $P < .0001$. Use of thiazide diuretics was the strongest independent predictor for the presence of falls or syncope at presentation to the ED even after correction for concomitant hyponatremia or hypokalemia (OR 1.78, 95% CI: 1.55-2.05, $P < .0001$). Moreover, increasing age was an independent risk factor for presence of syncope and falls (OR 1.03, 95% CI: 1.03-1.03, $P < .0001$), and there was a trend for male sex being protective (OR 0.91, 95% CI: 0.82-1.0, $P = .051$).

DISCUSSION

In the present analysis of a large collective of interdisciplinary emergency patients, thiazide diuretics were found to be commonly prescribed with an overall prevalence of roughly 8%. Patients taking thiazides were significantly and relevantly older than patients without thiazides and had more antihypertensive comedications, mostly inhibitors of the renin-angiotensin-aldosterone system. The prevalence of hyponatremia was high in patients taking thiazides, with more than 1 in 5 patients presenting with it. With a prevalence of 19%, hypokalemia was almost as frequent as hyponatremia. Moreover, it was shown, that the likelihood of hyponatremia and hypokalemia rose with increasing doses of thiazides. Additionally, there was a vast difference in the likelihood for hyponatremia and hypokalemia between the various thiazide types, with hydrochlorothiazide showing the least likelihood and chlorthalidone the highest with ORs of 7.63 (95% CI: 3.46-16.84) for hyponatremia and 22.7 (95% CI: 9.26-55.79) for hypokalemia. Syncope and falls on admission to the ED were significantly more common in patients taking thiazide diuretics, and in the multivariable regression analysis, they were independent predictors even after correction for presence of hyponatremia and hypokalemia. Increasing age was an independent risk factor for presence of syncope and falls (OR 1.03, 95% CI: 1.03,1.03, $P < .0001$), and there was a trend for male sex being protective.

The high prevalence of hyponatremia and hypokalemia in the present collective of patients taking thiazide diuretics stands in line with previous studies on the issue.[3,13] The mechanisms leading to hyponatremia in patients taking thiazides are complex and not completely understood as outlined and summarized in a recent review on the subject.[1] More recently, genetic predispositions for thiazide-associated hyponatremia were described.[14,15] Hypokalemia might in part be explained by significant potassium losses resulting from thiazide intake, although many patients had concomitant medication with an inhibitor of the renin-angiotensin-aldosterone system.[10] Also genetic predisposing factors were identified for hypokalemia.[16]

Previous studies support our current findings that hyponatremia and hypokalemia in patients with thiazide diuretics are significantly more likely in elderly as well as in female patients.[6,17] This stronger predisposition for women to develop dyselectrolytemias with thiazide diuretics might originate from biological gender differences: In 1994, Chen et al[18] found a significantly higher density of renal thiazide receptors in female compared to male rats. Furthermore, they detected a decrease in thiazide receptors of >20% after ovariectomy, attributing a pivotal role to female sex hormones. Only recently, female mice exposed to hydrochlorothiazide displayed an increased sodium excretion in comparison with male mice, while hydrochlorothiazide-induced potassium excretion showed little sex differences. Interestingly, on a high-potassium diet, male mice proved increased potassium secretion and greater distal sodium delivery, indicating an association of more efficient adaptation to potassium intake with male sex.[19] However, specific causes for the higher prevalence of the discussed electrolyte disorders remain unclear but may be linked to hormonal mechanisms and, thus, warrant further investigation. A simple tool for the prediction of the occurrence of hyponatremia in patients taking thiazide diuretics for arterial hypertension was suggested integrating 6 clinical factors including age >65 years as well as female sex.[20] Based on these findings, a "silent epidemic of thiazide-induced hyponatremia" was discussed.[21] Especially in elderly women, it is justified to avoid thiazide medication if feasible, and if prescribed newly, narrow monitoring of electrolytes is indicated.

In the present analysis, a thiazide dose-dependent effect was shown for both hyponatremia and hypokalemia. This finding is supported by previous studies; however, the literature remains discordant.[22] Nevertheless, this finding supports the causal role of thiazide diuretics in the genesis of hyponatremia and hypokalemia.

The at-first glance counterintuitive finding that both hypo- and hyperkalemia were more prevalent in patients taking thiazides might be explained by the fact that chronic kidney disease, the number-one risk factor for hyperkalemia, was more prevalent in this group.[23] The finding of increased hypokalemia is well-explained by the mechanism of action of thiazides where increased distal tubule sodium load stimulates potassium secretion and, consequently, excretion.[24]

The various types of thiazides showed markedly different risks for the presence of hyponatremia and hypokalemia: Although hydrochlorothiazide appeared to have the lowest likelihood, while still relevant and highly significant, chlorthalidone on the other end of the spectrum had by far the highest ORs for presence of hyponatremia and hypokalemia in our collective. This finding might be explained by the shorter plasma half-life of hydrochlorothiazide and might guide the choice of thiazide type when newly prescribing the medication for a patient.

One of the central findings of the present study is the significantly higher prevalence of falls and syncope in patients taking thiazide diuretics. This was also found in the multivariable regression analysis and remained highly significant even after correction for presence of hyponatremia, hypokalemia, age, and sex. This finding appears plausible on the basis of the mechanism of action of thiazide diuretics: Slight hypovolemia is possible, potentially leading to orthostatic hypotension and gait disturbances, predisposing both syncope and falls, which may even be aggravated by hyponatremia. Hence, it appears worth conducting further studies on this intriguing discovery.

Not surprisingly, patients taking thiazide drugs were older and had more antihypertensive agents as comedication indicating higher morbidity. Still, the effects of thiazides on the likelihood of hyponatremia and hypokalemia as well as the presence of syncope and falls remained highly significant even after correction for age and other cofactors underlying an independent effect.

Our findings imply an unfavorable effect of thiazide medication in elderly patients: This specific group is more prone to developing electrolyte disorders when taking thiazide diuretics[25,26] and, in turn, is again more prone to syncope and falls with thiazides as supported by our current findings. Together with the comparably recent findings of hyponatremia-induced osteoporosis, a more careful approach to prescribing thiazides in this vulnerable patient collective is wise.

Limitations

The present study is limited by its cross-sectional design. Moreover, due to a lack of data regarding the hydration status of the patients on ED admission, classification of volume status would have been rather speculative; therefore, further analysis of the exact mechanisms for hyponatremia and hypokalemia were not feasible.

CONCLUSIONS

Hyponatremia and hypokalemia are common findings in this large collective of patients taking thiazide diuretics occurring in approximately 1 in 5 patients. Thiazides were independently associated with electrolyte disorders and a dose-dependent effect was found with a variance in the likelihood of the presence of hyponatremia and hypokalemia depending on the type of thiazide. Syncope and falls were significantly more common in patients taking thiazides, and the drugs were independent predictors for these complications even after correction for age and presence of hyponatremia and hypokalemia. For all these reasons, a more careful approach to prescribing thiazides in the older adult seems wise.

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