Difficulties in treatment with thiazide diuretics in the elderly

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Abstract

Thiazides are in common use also in people over 65 years of age. Their side effects before the age of 60 are not very common and usually refer to the development of hypokalemia. In the elderly, the number of complications after thiazides increases significantly, and the most common side effect is hyponatremia. Although mild hyponatremia is usually asymptomatic, more severe cases may cause weakness, appetite loss, nausea, vomiting, and dizziness. However, even asymptomatic hyponatremia increases mortality. The therapy depends on the clinical picture and requires a reduction in fluid intake (in patients with symptoms of inadequate vasopressin secretion) or hydration and administration of salt solution (in patients with symptoms of decreased extracellular space). The treatment with thiazides may increase the risk of skin cancer due to fotosensibilsation.

Key words: thiazides; hyponatremia; hypokalemia; squamous cell carcinoma

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Introduction

Thiazide drugs were first introduced into medicine in 1957. These drugs have proved effective in the treatment of high blood pressure, and their side effects are relatively small. For more than half of the previous century, thiazides have been used in the treatment of hypertension and congestive heart failure and are still among the most frequently prescribed medications [1]. Like many other drugs, thiazides have side effects [2], such as commonly known hypokalemia. Nevertheless, in the elderly there have been many reports of a frequent and dangerous course of hyponatremia following the use of thiazides [2–7]. Since thiazide associated hyponatremia is a rare complication in young people, this complication is underestimated by most doctors. In the recent European guidelines for the management of arterial hypertension, the diuretic section, hyponatremia was not mentioned after thiazide use [1]. For this reason, we decided to present the epidemiology, pathogenesis and symptoms of hyponatremia in elderly people treated with thiazides [4, 7]. In the final part of our article, we discussed recent reports of an increased risk of skin cancer development in seniors using thiazides, and especially of a higher incidence of squamous cell carcinoma of the skin [8].

Hyponatremia

Reduced blood sodium concentration below 135 mEq/L is considered mild hyponatre-

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mia, with reduced sodium concentration below 130 mEq/L moderate hyponatremia is diagnosed, and finally, sodium concentration below 120–125 mEq/L can be life-threatening and considered severe hyponatremia.

Epidemiology of thiazide associated hyponatremia

Recently, more attention has been paid in the literature to the development of hyponatremia in elderly patients, including those with arterial hypertension [2–7]. According to many authors, hyponatremia in the elderly is the most common electrolyte disturbance found in both hospitalized and non-hospitalized patients, and one of the important causes is diuretic therapy. In the Zhang and Xiao-Ying cohort study, 17,693 patients over 80 years of age were admitted to the hospital in Beijing within 3 years [7]. Patients with hyponatremia accounted for 24.7% of this age group admitted to the hospital. The comorbidities were pneumonia and chronic obstructive pulmonary disease, cancer, cardiovascular and neurological diseases. Diuretics were used in 57.4% of patients. In-hospital mortality in patients with mild hyponatremia was 8.9%, in patients with moderate hyponatremia — 15.6% and in those with severe hyponatremia — 20.7%. According to Clayton et al. 14% of patients treated with thiazides develop hyponatremia (sodium concentration below 135 mmol/L), and in people over 70, the risk increases even more [9]. According to other authors, hyponatremia develops after the use of thiazides in 4 to 14% of patients, and in the elderly up to 30% of patients treated with this drug. For example, in a study by Elmi et al., among 2034 patients admitted to the hospital with routine electrolyte levels and plasma osmolality, hyponatremia was found in 384 (13.9%) patients [18]. The median of people with hyponatremia was 79 years (range 27–100 y). In the group of patients studied by Elmi et al., in 82% of patients with low level of sodium, hyponatremia was asymptomatic. In symptomatic patients, weakness, nausea, or neurological symptoms predominated. Symptoms of vomiting, falls, and confusion were more common in women than in men with hyponatremia. Many authors reported more frequent occurrence of hyponatremia in older women than in men [11, 12]. The incidence of hyponatremia in geriatric clinics ranged from 18% to 22%, but asymptomatic hyponatremia was often undiagnosed. Rodenburg compared 3556 patients receiving thiazides and 9769 not receiving these drugs and showed that the risk of hyponatremia in the first group was almost 5 times higher; and there was 8 times higher risk for the development of severe hyponatremia [13]. In another study of patients with arterial hypertension and hyponatremia, it was observed that only 10% of these subjects received doses of thiazides (hydrochlorothiazides) lower than 12.5 mg/day, the others on average 35 mg/day (some of them even more than 50 mg/day) [14]. Life-threatening hyponatremia may appear after 2 days of using thiazides, but usually occurs much later, even after many years of such treatment. According to Leung et al. the median onset of hyponatremia is 1.75 years of using thiazides. However, 37% of the respondents stated that they had used thiazides for more than a year, and only after that time did they develop hyponatremia [15]. Thiazide-like diuretic namely, indapamide may also cause hypokalemia and hyponatremia. According to Chapman et al. the incidence of hypokalemia after using indapamide is as high as 20.9%, and of hyponatremia 21.7% [16]. A retrospective analysis of 730, 225 patients showed that treatment with older thiazide-like diuretic i.e.: chlorthalidone, resulted in a higher risk of hyponatremia [hazard ratio (HR): 1.31] when compared with hydrochlorothiazide [17]. The Liang meta-analysis showed that the risk of hyponatremia and hypokalemia is the same for hydrochlorothiazide and indapamide [18].

Pathogenesis of thiazide-induced hyponatremia.

A concept of a thiazide associated hyponatremia (TAH) and thiazide induced hyponatremia (TIH) has been recently discussed [19, 20]. The pathogenesis of TIH is not thoroughly clear. A genetic predisposition has been documented in some patients [21–23]. As thiazides are known to act on the distal renal tubule, which dilutes the urine by blocking the counter-transportation of a sodium chloride. This leads to an increased excretion of sodium, while the excretion of "free" water is reduced. The retention of "free" water in the blood serum results in the reduction of sodium concentration [21]. Thiazides reduce the extravascular space, thus an increased secretion and/or increased sensitivity to antidiuretic hormone (ADH) to their action is considered. Increased activity of the ADH, in turn, enhances the reabsorption of "free" water in the kidneys [21]. Recent stud-

ies by Frenkel et al., however, showed that thiazides block the secretion of the antidiuretic hormone, while they observed increased secretion of the prostaglandin E2 (PGE2) in the urine [24]. This prostaglandin plays an important role in the renal reabsorption of water in the renal tubules [25]. In addition, the use of diuretics often causes hypokalemia. Hypokalemia increases the penetration of sodium into the intracellular space and reduces the concentration of sodium in the blood serum. The phenotypic picture of TIH may vary from patient to patient. Participation is contemplated in the excessive water intake, impaired free-water excretion, solute depletion, osmotic inactivation of cations [21]. The contribution of the individual pathophysiological factors mentioned above may differ from person to person [19]. Genetic predisposition was demonstrated only in some patients. According to Ware et al. and Huang et al. certain genetic polymorphisms acting on apical prostaglandin transporter of the distal nephron or renal outer medullary potassium channel (ROMK) could play its role in susceptible individuals [19, 22, 23]. In patients over 65 years of age, other factors additionally exacerbate thiazide-induced hyponatremia (TAH). In Burst's observation, 118 among 477 patients with euvolemic hyponatremia (NA < 130 mEq/L) treated with thiazides met the criteria of true thiazide-induced hyponatremia [20]. This means that in 358 patients, hyponatremia was caused by other etiological factors in addition to thiazides. Many elderly patients use non-steroidal anti-inflammatory drugs and proton pump blockers, which may also lead to hyponatremia [26, 27]. Many neurological and psychiatric medications often prescribed to seniors are known to have side effects of severe hyponatremia. These drugs include benzodiazepines, serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), and anti-epileptics [28]. According to Grattagliano, patients using 6 drugs simultaneously, developed hyponatremia six times more often than patients treated with one drug [29]. Patients with hypertension are recommended a low-sodium diet. Anbari et al. recently showed that perceived intensity of saltiness perception in hypertensive patients is higher than in control group [30]. In the period of hyponatremia, people with hypertension may not feel the need to add salt to the food. Inflammation of the lungs and lung cancer are known causes of inadequate secretion of vasopressin. One of the rare causes of hyponatremia is the syndrome referred to in the Anglo-Saxon literature as "Tea and toast". This syndrome develops in elderly patients with renal failure. These patients remain on a low-protein, low-sodium diet and drink plenty of fluids. Due to high fluid consumption and low sodium levels, renal tubular water reabsorption is increased and hyponatremia develops [31]. Other causes of hyponatremia are pituitary and adrenal insufficiency (Addison's disease). Ishikawa et al. reported that 40% of elderly hyponatremic patients have pituitary adrenal dysfunction [32]. In elderly patients, the concentration of vasopressin in the blood serum also increases, which increases the possibility of developing the syndrome of inappropriate ADH secretion (SIADH). Autonomic thyroiditis, which leads to hypothyroidism, is also common in seniors. Severe thyroid insufficiency may develop a syndrome of inadequate vasopressin excretion, characterized, inter alia, by hyponatremia. Many elderly patients are diagnosed with type 2 diabetes which, if poorly controlled, may promote osmotic diuresis along with the loss of sodium [6]. The use of thiazides in patients with the above-mentioned risk factors increases the frequency and worsens the electrolytes imbalance.

Symptoms and prognosis of hyponatremia

Very often, hyponatremia is asymptomatic. The most common symptoms of hyponatremia are headache, apathy, loss of appetite, and nausea. In more advanced hyponatremia, vomiting, disturbances of consciousness, convulsions and finally coma may be observed [2, 3]. Relatively recently, it has been shown that patients with hyponatremia fall more often, and osteoporosis develops more frequently in their skeletal system. In elderly patients, the symptoms of hyponatremia may resemble the frailty syndrome [33, 314]. Adams et al., in a large retrospective study of 341,003 patients, assessed the incidence of osteoporosis in people over 55 years of age [35]. In these subjects, serum sodium concentrations were measured at least twice before densitometry. In subjects with concentrations of this ion below 135 mmol/L, osteoporosis occurred in 59.7% while in those without hyponatremia it occurred in 43.9% ($p < 0.0001$). Bone fractures that appear after minor trauma are much more common in the elderly with even mild hyponatremia than in those of the same age with normal serum sodium levels.

Hyponatremia in old age is often asymptomatic or atypical in the form of osteoporosis and cognitive impairment, widely known as frailty syndrome [34, 36].

Klhufek and Salek compared the clinical and laboratory results in 282 patients with non-thiazide-induced hyponatremia and in 143 patients with TAH [19]. In the latter, the patients were older, women predominated, more often complained of weakness, nausea, vomiting, diarrhea and confusion. Several studies have shown that hyponatremia is an independent risk factor for death [37, 38]. The Corona meta-analysis [38] showed that correction of asymptomatic hyponatremia also reduces the risk of death. The necessity of asymptomatic chronic therapy is indicated by studies which show a higher incidence of osteoporosis [35] and mild cognitive impairment [34, 37], and above all a higher risk of death [38]. In the group of patients studied by Elmi et al., in-hospital mortality was 4.7%, while in patients with hyponatremia it was 8.5% [10]. Among 220 patients treated with thiazides, Leung et al. found moderate hyponatremia (Na < 130 mmol/L) in 30%, and in 10.6% of patients, severe (Na < 129 mmol/L) hyponatremia [15]. In patients with sodium levels below 138 mmol/L, each 1 mmol sodium drop increases mortality by 8 to 20%. According to Tzoulis et al., in patients with sodium concentration below 128 mmol/L, the risk of death during hospitalization is 3.3 times higher than in patients with sodium concentration above 128 mmol/L [37]. Several studies summarized in the meta-analysis by Chen et al. have shown that hyponatremia is a significant unfavorable prognostic factor both in short- and long-term follow-up [39].

Hyponatremia risk factors

Serum sodium deficiency in hypertensive patients treated with thiazides may appear at any age, but the elderly are the most vulnerable [10, 11, 19]. Another risk factor for the development of hyponatremia is the genetic predisposition [21–23]. Several studies have shown that female gender, smoking, alcohol consumption and a relatively low patient's BMI are significant risk factors for the development of hyponatremia [19, 21].

This electrolyte imbalance is significantly more common in white people. It has also recently been noticed that high serum high-density lipoprotein cholesterol (HDL-C) may precede the onset of hyponatremia. The relationship between high HDL concentration and hyponatremia has been studied in detail by Israel and Grossman [40]. According to these authors, among patients with HDL-C cholesterol levels greater than 62 mg/dL, the risk of developing hyponatremia was 3.7 times higher than in patients with low levels of this cholesterol. Multivariate analysis showed that the observed relationship between HDL-C and hyponatremia was independent of the age of the subjects. The cited authors also analyzed the results of the National Health and Nutrition Examination Survey in the United States (NHANES) conducted in 2005–2010. This study measured the concentration of sodium in the blood and the concentration of HDL-C in 16,501 people over 18 years of age. Sodium levels below 132 mmol/L were found in 135 patients. At the same time, these people showed a high concentration of HDL-C. The relationship between high HDL-C and low sodium concentration in the multivariate statistical analysis turned out to be independent of the age and sex of the patients and possibly concomitant diabetes. The mechanism of the relationship between HDL-C and hyponatremia is not clear.

Diagnosis of hyponatremia

The measurements of sodium concentration in the blood require including several factors into consideration to properly report the actual natremia (e.g., high glucose levels). For every 100 mg/dL excess in blood glucose concentration a 1.6 mmol/L should be added to the measured sodium concentration. Pseudohyponatremia may also occur in patients with hyperproteinemia (e.g., multiple myeloma) and in patients with very high cholesterol and triglycerides [6].

Hyponatremia is also often classified as acute, that is developing within 48 hours, or chronic, gradually increasing. The number of 48 hours is not an absolute value, it depends on how long cells adapt to intercellular fluid hypotension. Acute and profound hyponatremia threatens to rapidly develop cerebral edema. Conversely, rapid correction of sodium levels in chronic hyponatremia may lead to demyelization of the brain. The distinction between acute and chronic hyponatremia is not always easy, the more so as the clinical symptoms may be similar [41]. For this reason, the distinction between symptomatic and asymptomatic hyponatremia is more often used. The latter is also associated with an increased risk of death.

A study by Kanchansuraki et al. provided practical recommendations how to assess the risk of hyponatremia in hypertensive patients receiving hydrochlorothiazide [42]. The authors of this study propose to use the ABCDEEF-S score (where A is age, B — benzodiazepines, C —cerebral lesion, D — dose of hydrochlorothiazide, F — female sex and S — statin use). The query helps to estimate which patients are more predisposed to develop hyponatremia. Interestingly, the use of statins reduces the likelihood of this condition.

Hyponatremia in patients treated with thiazides may have two different biochemical profiles, namely with decreased extracellular volume or normovolemic – resembling SIADH [6]. It is difficult to distinguish between the two forms of hyponatremia [19]. In the SIADH the concentration of ADH hormone is higher than the current demand of the system. However, increased levels of the antidiuretic hormone have not always been found in the case of TAH, resembling Bartter Schwartz syndrome [23, 24]. To diagnose a SIADH, low plasma osmolality (< 280 mOsm/kg H2), low serum sodium (< 130 mmol/L) and urine sodium concentration greater than 40 mmol/L should be demonstrated. The concentration of uric acid in the blood serum may be helpful in differentiating between decreased extracellular volume and Schwartz-Bartter syndrome. Uric acid concentration below 4 mg/dL and urea concentration below 20 mg/dL in the blood serum indicate hyponatremia in the course of inadequate vasopressin secretion [6], while uric acid levels above 4 mg/dL indicate a decreased extracellular volume. This differential test should be performed during the serum sodium recovery period. These data should be treated with caution in the elderly, in whom it is often difficult to differentiate between SIADH and hypovolemic hyponatremia. Filippatos et al. propose to administer 1–2 liters of 0.9% NaCl solution intravenously over 1–2 days. An increase in blood sodium concentration > 5 mmol/L with a simultaneous only minimal increase in fractional sodium excretion indicates hypovolemic hyponatremia [6]. On the other hand, a slight increase in the concentration of sodium in the blood or even its decrease in the blood may indicate the SIADH syndrome.

In the course of thiazide therapy, low levels of sodium in the blood serum may additionally be caused by insufficient intake of table salt, which may lead to hyponatremia with reduced extracellular space, or the development of SIADH syndrome in the course of normal circulating blood volume.

Therapy of hyponatremia

The therapeutic management differs between patients with symptoms of SIADH and patients with hypovolemic hyponatremia, but the diuretic should always be discontinued. Burst et al. observed that in US and EU hospitals, the thiazide that caused hyponatremia was discontinued on the first day after diagnosis in only 57% of cases, and in 30% it was still administered despite sodium levels below 130 mmol/L [20]. In SIADH syndrome, the intake of fluids should be reduced in order to increase the concentration of sodium in the blood serum [43, 44]. The amount of ingested fluid should be equal to the daily urine volume minus 500 mL. If the blood sodium concentration does not increase after 48 hours, and also in patients with severe hyponatremia, it is advisable to increase the sodium intake orally or intravenously.

Hyponatremia in the course of hypovolemia should be treated with adequate fluid intake to avoid stimulation of ADH secretion [6]. For this purpose, intravenous infusions of saline are used. In order to avoid overhydration, a small dose of furosemide (20–40 mg) can be administered. Furosemide increases the excretion of „free water" and thus increases the concentration of sodium in the blood serum [6]. Such management is especially indicated in patients with heart failure. In patients with acute hyponatremia, a 3% saline solution is usually administered intravenously to prevent severe neurological symptoms (seizures). However, too fast correction of sodium concentration in the blood serum may lead to dangerous consequences in the form of the osmotic demyelization syndrome (ODS) [45]. The increased risk of this syndrome concerns malnourished patients, patients with potassium deficiency, with advanced liver disease due to alcoholism. In order to avoid this syndrome, frequent determination of sodium concentration in the blood serum is recommended, e.g., every few hours, and slow sodium supplementation, e.g., 6–8 mEq/L within 24 hours. Burst et al. analyzed the treatment of thiazide-induced hyponatremia (Na < 130 mEq/L) in 477 patients, most of them over 65 years, in US and EU hospitals. The most common treatment used was isotonic NaCl solution (29.6%), fluid restriction (19.9%), a combination of both treatments, first with concentrated salt and then fluid restriction (8.2%) and administration of hypertonic saline 5.2%. Fluid restriction was markedly less effective [20]. Only in 57 patients, thiazides were discon-

tinued on the first day of hyponatremia therapy [20]. A detailed discussion of the treatment of hyponatremia can be found in the publications of Spasowski et al and Verbalis et al. [43, 44].

Hypokalemia and hypomagnesemia

It was early noticed that thiazides can cause hypokalemia, and doctors often order blood potassium measurements in patients treated with these drugs. The most common symptoms of hypokalemia are weakness, loss of appetite, confusion, falls, dizziness and headache, insomnia or somnolence, hallucinations, and finally coma [46].

The study by Vuliame showed that in 10% of patients admitted to the intensive supervision unit due to hypokalemia, their serious condition was caused by the use of thiazides [46].

In a review by Lin et al. published this year (2022), the occurrence of hypokalemia in patients treated with thiazides was estimated at 7% to 56% [47]. The use of high doses of thiazides as well as other drugs at the same time may increase the incidence of this dyselectrolytemia. The incidence of hypokalemia is higher in women and black people [48]. This electrolyte disturbance can lead to arrhythmias and increased mortality [49].

The diagnosis of hypokalemia is easy, because the assessment of electrolytes is one of the basic tests both in the hospital and in open treatment. The lowered potassium level causes flattening of the T wave with a distinct U wave, as well as lowering the ST-T segment. Long-term (over a year) use of thiazides in the general population leads to hypomagnesemia [50]. Hypomagnesaemia, in turn, increases the risk of developing cognitive impairment [51].

Oral potassium supplementation or the addition of a potassium-sparing diuretic is sufficient in most cases to prevent hypokalemia. Limiting the consumption of table salt and increasing the consumption of vegetables and fruits will reduce both arterial hypertension and hypokalemia [52].

Carbohydrate, cholesterol and uric acid metabolism

The use of thiazides can also disturb the carbohydrate and cholesterol balance. In a meta-analysis by Mukete and Rosendorff, including 10 randomized clinical trials and over 17,000 patients, blood glucose levels increased by 3.6 mg/dL during thiazide therapy, and potassium levels fell by 0.22 mEq/L. The increase in glucose after thiazide therapy is slightly larger in women. This increase in serum glucose has not been reported to be of clinical significance [53].

Spence et al. assessed blood lipids during treatment with thiazides. The concentration of cholesterol and its fractions did not change significantly, while the concentration of triglycerides increased significantly more with indapamide than with cholesterol [54].

Therapy with thiazides may also cause a statistically significant increase in uric acid levels. According to the studies of Ohta et al., the increase in blood uric acid concentration in patients by more than 1 mg/dL after administration of indapamide is associated with the initial higher systolic arterial pressure and higher blood glucose concentration [55].

In the analysis of the causes of gout, a significant role of diuretics, including thiazides, has been demonstrated [56]. These drugs should be avoided in patients with hypertension and diagnosed gout. Due to the fact that the attacks of gout are more frequent in the elderly [57] the therapy with thiazides of elderly patients with arterial hypertension may more often cause the symptoms of gout.

Skin tumors

Squamous cell carcinoma (SCC) of the skin accounts for 20% of all skin cancers, and the United States alone is diagnosed with 1 million cases of this cancer each year. Analyzing the UK database, Schneider et al. demonstrated a statistical relationship between hydrochlorothiazide intake and skin squamous cell carcinoma [58]. The use of this drug almost doubled the risk of this cancer, the use of indapamide increased the risk of melanoma by 40%, and treatment with bendroflumethiazide did not increase the risk of this cancer. Recent European and American studies also indicate an increased risk of skin cancers associated with the use of hydrochlorothiazide [59]. Daniels B et al. tested similar relationships in Australia where is the highest incidence of skin cancer in the world, and at the same time a high percentage of elderly Australians are treated with hydrochlorothiazide for hypertension or heart failure [60]. The use of this drug in the usual doses increased the risk of SCC of the lips by 260%, and in people, who received a total of 25,000 mg of this drug, the risk of developing cancer more than quadrupled. Concurrently, the use of thiazides increased the incidence of melanoma by 20%. According to O'Nell,

the risk of developing squamous cell carcinoma increases depending on the dose and duration of hydrochlorothiazide use. For example, five-year use of this diuretic increases the risk by 3 to 4 times [61].

A meta-analysis by Shao et al. showed that the use of hydrochlorothiazide increases the risk of SCC by 32%, and melanoma by 11% [8]. No meaningful increase in the risk for skin cancers was associated with bendroflumethiazide and indapamide [8]. On the other hand Schneider et al. showed that indapamide significantly increases the risk of developing melanoma [58]. Feinstein et al confirmed earlier observations that hyponatremia is often a perioperative complication of squamous cancer of the scalp and neck. Probably some of these patients were treated with thiazides, which caused skin cancer and increased the likelihood of hyponatremia [62].

Renal cell carcinoma

Diuretic therapy (mostly thiazides) might increase the risk renal cell cancer in women as reported in the study by Hiat et al. [63]. In the most recent Doth meta-analysis from 2000, there were only few studies suggesting a link with hydrochlorothiazide use and kidney cancer, mainly in women [64]. Kidney cancer most often occurs in a transplanted kidney [65]. The use of hydrochlorothiazide in kidney transplant patients may be an additional risk factor for the development of this cancer [66] .

Other skin complications

Treatment with thiazides, especially in the elderly, can also cause numerous non-tumor skin lesions. There have been reports of multiple forms of thiazide induced rash, such as lichenoid lesions, cheilitis, petechiae photo-onycholysis, photoleukomelanoderma and persistent photosensitivity conditions [67].

Prevention of side effects

Hyponatremia is a disease primarily of the elderly. For this reason, in these patients, caution should be exercised in administering drugs that may cause hyponatremia. In patients with arterial hypertension, more frequent use of calcium antagonists with angiotensin converting enzyme inhibitors is indicated, and less frequent use of thiazides. In patients with refractory arterial hypertension, first try low doses of thiazides, e.g., hydochlorothiazide. Combining thiazides with certain antidepressants should be avoided; however, bupropion or mirtazapine are allowed [68].

It should be underscored that in a large cohort of 13,500 patients over 45 years of age, the use of thiazides was associated with a fivefold increase in the risk of developing hyponatremia as compared to diuretics-naïve patients [13]. There are suggestions, that thiazides may be replaced with loop diuretics, which less frequently leads to hyponatremia [69]. High cumulative doses of thiazides predispose to SCC. Elderly patients administered with thiazides should be cautioned against overexposure to the sun. Discontinuation of thiazides should be considered in patients with gout and in patients with transplanted kidneys.

Conclusion

According to the current (as well as previous) recommendations of experts, diuretics (including hydrochlorothiazide) are still the basic drugs in the treatment of hypertension. They are used primarily for many years in patients with arterial hypertension or heart failure, diseases very common after the age of 65. These drugs, however, can lead to long-undiagnosed hypokalemia in the elderly.

However, the most common and possibly life-threatening electrolyte imbalance in the elderly is hyponatremia. There are many causes of such condition in this group of patients, yet frequent thiazide therapy may play quite important role. Even symptomless hyponatremia increases mortality, therefore particular caution should be taken especially in elder patients. Skin cancers including squamous cell carcinoma may also be attributed to chronic use of thiazides. Use hydrochlorothiazide is associated with an increased risk of SCC and with evidence of duration and dose response relationship. Elders treated with thiazides should be instructed not to expose excessively to sun and encouraged to undergo periodic dermatological tests. In patients with kidney transplantation or gout, thiazides should be replaced with other diuretics, if possible.

Diuretics, and in particular thiazide drugs, are extremely helpful in the treatment of hypertension [70]. Its' addition to ongoing blood pressure lowering therapy allows to overcome resistance to therapy [70]. Nevertheless physicians should pay particular attention to possible side effects of these drugs, especially in the elderly.

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