Review Paper

The Silent Epidemic of Thiazide-Induced Hyponatremia

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Hyponatremia is a recognized complication of treatment with thiazide diuretics, particularly in patients older than 70 years. Severe and symptomatic hyponatremia requires urgent management, usually requiring infusion of normal or hypertonic saline. Milder, asymptomatic, thiazide-induced hyponatremia requires steps to manage the hyponatremia as well as to prevent its future recurrence. This is a particular problem in patients who despite a history of thiazide-induced hyponatremia might require a diuretic in the management of their hypertension. In this review, the acute management of symptomatic and asymptomatic thiazide-induced hyponatremia is reviewed. Emphasis is also placed on the chronic management of patients who have experienced mild hyponatremia, in whom decisions about treatment with diuretic and nondiuretic antihypertensive agents must be made to satisfy the twin goals of controlling hypertension and avoiding recurrent hyponatremia. J Clin Hypertens (Greenwich). *2008;10:477–484.* ©*2008 Le Jacq*

Considerable attention is paid to the problem of thiazide-induced hypokalemia. Much less attention is paid to thiazide-induced hyponatremia (TIH), which is seen with considerable frequency. TIH occurs predominantly in the elderly.[1–4] As a result, it is not encountered in the data of large drug treatment trials that involve predominantly younger patients. However, in the Systolic Hypertension in the Elderly Program (SHEP), which focused on older patients, hyponatremia (defined as a sodium level <130 mEq/L) was observed in 4.1% of patients treated with chlorthalidone vs 1.3% in the control group, while hypokalemia (potassium level <3.2 mEq/L) was observed in 3.9% of patients in the treatment group.[5] Thirty percent of patients were receiving 12.5 mg of chlorthalidone, and 60% were receiving 25 mg.[5] In another study in the elderly, diuretic-induced hyponatremia, defined as a serum sodium concentration ≤130 mEq/L, was seen in 17% and hypokalemia in 6.6%.[6] Fifty-three percent of patients were receiving a thiazide diuretic and 24% a loop diuretic.[6] In patients with TIH, an average daily hydrochlorothiazide dose of 35 mg has been reported, with 44% of patients having received ≥50 mg.[7] However, in 10% of cases the dose was only 12.5 mg.[8] The risk of TIH is 3-fold higher in persons older than 70 years and is higher among women, possibly because of smaller body size or lower sodium intake.[2,3] With the high prevalence of hypertension in the elderly and the routine use of thiazide diuretics to treat it, TIH is clearly a prevalent problem.

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CLINICAL PRESENTATION

TIH can develop acutely or gradually. It can range from mild to severe and from asymptomatic to symptomatic. The onset is within 2 weeks of starting the diuretic in 50% to 90% of cases, but it can occur within a day or two or even after a single dose.[3,7–9] Hyponatremia can occur after months or years of taking a thiazide and is likely related to subsequent contributory factors such as reduction of

Table I. Thiazide-Induced Hyponatremia: Contributory Mechanisms
1. Thiazide effects
Reduction in free water clearance
Renal sodium loss
Stimulation of antidiuretic hormone secretion
Potassium depletion
2. Patient characteristics
a. Reduced renal capacity to excrete free water, usually age-related
b. Excess free water intake
i. Increased water intake
Low salt intake
c. Ingestion of other drugs that affect free water clearance

renal function with aging, ingestion of other drugs that affect free water clearance, or changes in water or sodium intake. Mild hyponatremia, with serum sodium concentration in the range of 125 to 132 mEq/L, is usually asymptomatic, although vague symptoms such as fatigue or nausea are possible. More severe hyponatremia, as reported in patients who required hospitalization, can be asymptomatic or associated with symptoms including weakness (39.4%), vomiting (37.8%), nausea (26.7%), confusion (16.7%), dizziness (15%), abdominal pain (12.2%), and manifestations as serious as lethargy, seizures, and coma.[7] Neurologic sequelae from either cerebral edema or central pontine myelinosis are possible, as discussed below. Mortality appears related more to underlying conditions than to hyponatremia per se.

PATHOPHYSIOLOGY

The 3 main factors that determine the risk of TIH are water intake, capacity of the kidneys to excrete free water, and presence or absence of antidiuretic hormone (ADH). The involvement of each may differ from case to case.

TIH occurs when the intake of free water is greater than the amount the kidneys are able to excrete. In individuals whose kidneys' ability to excrete a free water load is moderately reduced, a thiazide will cause hyponatremia if fluid intake is excessive. In those in whom the kidneys' ability to excrete a free water load is markedly reduced, hyponatremia can ensue even with ordinary fluid intake. The third factor, ADH, likely plays a role in some cases but not others, as discussed below.

It is important to distinguish hypovolemic from nonhypovolemic TIH. In patients with hypovolemia, ADH is stimulated and contributes to reduced free water excretion. In contrast, in euvolemic or hypervolemic patients, ADH is usually suppressed and is not contributory. Thus, although both ADH secretion and excess water intake can contribute to TIH, neither is a sine qua non of the disorder.

The development of TIH is dependent on both thiazide-related effects and patient factors that govern susceptibility to developing TIH (Table I).

THIAZIDE EFFECTS

The effect most responsible for TIH is thiazide-induced reduction of free water clearance by the kidneys. Thiazide diuretics interfere with maximum dilution of urine by blocking sodium chloride cotransport in the distal tubule, the main diluting site in the kidney. Excretion of sodium is increased, while excretion of free water is diminished.[10–12]

Thiazide diuretics, particularly at higher dosages, can also reduce intravascular volume and glomerular filtration rate, stimulating proximal reabsorption of fluid, which reduces delivery of fluid to the diluting sites and thus the amount of free water available for excretion. Reduced intravascular volume also stimulates secretion of ADH, which increases water reabsorption. Secretion of ADH is appropriate in defending blood volume, but it contributes to the development of hyponatremia. Potassium depletion due to a thiazide diuretic causes an intracellular shift of sodium, and some suggest that this contributes to TIH.[12,13] However, the importance of hypokalemia as a contributor to TIH is unclear because hyponatremia often occurs without hypokalemia, even when a potassium-sparing diuretic has been coadministered.[14,15] The association between TIH and hypokalemia is likely more prominent in patients receiving a high dosage of a thiazide.[13] At lower dosages, hypokalemia might play less of a role.

PATIENT FACTORS

Clearly, most elderly patients receiving a thiazide diuretic do not develop TIH. Two key patient-related factors associated with an increased risk of developing TIH are reduced ability to excrete free water and increased fluid intake.

The ability to excrete free water, as reflected in minimum achievable urine osmolarity, declines with age.[10] Even healthy adults recover more slowly from lowered sodium induced by a water load.[10] The capacity to excrete free water is even lower in elderly individuals with a history of TIH[10] and is indicative of a predisposition to develop hyponatremia upon exposure to a thiazide diuretic. A high fluid intake, >1.5 to 2 L/d, also predisposes to TIH by necessitating greater excretion of free water to

maintain eunatremia. The free water load is even higher in those who have both a high water intake and a low sodium intake.

Many persons consume excessive fluid, and many adhere to popular recommendations to consume ≥8 glasses of water a day or increase fluid intake because of a history of nephrolithiasis. Psychogenic polydipsia or polydipsia secondary to psychotropic medication can also be responsible. Of interest, individuals with a history of TIH, on rechallenge with a single dose of a thiazide, have been shown to gain rather than lose weight despite diuresis.[9] This suggests that a thirst disorder, leading to increased fluid intake, might be contributory.[9]

TIH is most likely to occur when a thiazide is given to individuals with a preexisting reduction in free water clearance or a high fluid intake or both, particularly if their sodium intake is low. The risk is obviously increased at higher doses of the thiazide diuretic.

THIAZIDE DIURETICS VS OTHER DIURETICS

Most reported cases of diuretic-induced hyponatremia are associated with a thiazide diuretic, although cases are also reported with loop diuretics and with spironolactone.[3,7] Underlying congestive heart failure, for which loop diuretics are the usual diuretic prescribed, is itself a risk factor for development of hyponatremia.

Thiazide diuretics are more likely to cause hyponatremia because their major effect is in the distal tubule, the major diluting site of the kidney. In contrast, the main effect of loop diuretics is in the ascending limb of the loop of Henle, which is a less important diluting site with less effect on maximum dilution.[11] At this site, loop diuretics also impair ability to concentrate urine, resulting in excretion of water in excess of sodium.[16] Loop diuretics have a shorter duration of effect and also reduce responsiveness to ADH; both effects reduce the risk of developing hyponatremia.[17] For all these reasons, loop diuretics would seem less likely to cause hyponatremia, consistent with reported observations.[3,18,19] And when hyponatremia does develop while taking a loop diuretic, it is more likely due to sodium loss than to free water retention, unless fluid intake is very high.[20]

Potassium-sparing diuretics act at the distal diluting sites, adding to the impairment of dilution associated with administration of a thiazide. These include the mineralocorticoid receptor antagonists spironolactone and eplerenone, as well as triamterene and amiloride, which act directly in the distal tubule. When administered in combination with a thiazide, these agents might increase the likelihood of hyponatremia.[14,16]

EFFECTS OF OTHER DRUGS

Several drugs increase the likelihood of developing TIH. Nonsteroidal anti-inflammatory drugs, through prostaglandin inhibition, decrease free water clearance.[21] Drugs such as chlorpropamide or selective serotonin reuptake inhibitors are associated with the syndrome of inappropriate antidiuretic hormone secretion, which predisposes to TIH. Polydipsia caused by psychotropic medications also predisposes to TIH.

COMPLICATIONS OF TIH

The 2 main neurologic complications of severe hyponatremia of any cause are cerebral edema and central pontine myelinosis. Cerebral edema is a direct result of acute hyponatremia, whereas pontine myelinosis is caused not by the hyponatremia but by overly rapid correction of hyponatremia. Fortunately, with appropriate care, most patients with TIH recover without neurologic sequelae.

Cerebral edema occurs in the setting of severe acute hyponatremia. A shift of fluid along an osmolar gradient results in intracellular edema and, at its extreme, increased intracranial pressure and brain herniation. Clinical manifestations, including obtundation, seizures, and coma, have been observed in patients with severe TIH.[22] In contrast, when the onset of hyponatremia is more gradual, compensatory extrusion from cells of sodium and potassium ions and organic osmolytes reduces the osmolar potential and prevents development of excess intracellular volume.[23] This lessens the risk of cerebral edema, reduces symptoms and, importantly, lessens the urgency with which the serum sodium level needs to be corrected. When hyponatremia develops gradually, particularly with sodium levels >125 mEq/L, it is generally asymptomatic.[24,25] However, when severe hyponatremia develops rapidly, symptomatic cerebral edema can ensue before the protective compensatory loss of cellular ions can occur.

The development of central pontine myelinosis, which has also been seen in patients with TIH, has been associated with excessively rapid correction of hyponatremia.[3,24] It is now clear that it is the overly rapid correction of serum sodium—at a rate faster than 20 mEq/L/d—rather than the hyponatremia itself that is largely responsible for most cases of pontine myelinosis.[3,24,26] Rapid correction can cause extrusion of intracellular fluid, cellular dehydration, and hyperosmolar demyelination in

Table II. Suggested Algorithm for Treatment of Thiazide-Induced Hyponatremia
Asymptomatic or minimally symptomatic thiazide-induced hyponatremia
Acute management
1. Withdraw the offending thiazide diuretic
2. Restrict fluid intake to <1 L/d or to <800 cc/d, if needed, to induce negative water balance
3. If hypovolemic, infuse normal saline or increase oral sodium intake, depending on the severity of the hyponatremia
Chronic management
1. Avoid habitually excessive fluid intake
2. Replace the thiazide with nondiuretic antihypertensive therapy or, if a diuretic is needed, with a loop diuretic
3. Carefully monitor serum sodium values
Symptomatic hyponatremia (usually <120 mEq/L)
1. Withdraw offending thiazide diuretic
2. If hypovolemic and only mildly symptomatic, infuse normal saline
3. If euvolemic or hypervolemic or if symptoms are severe, infuse hypertonic saline
a. Infuse hypertonic saline (3% NaCl;5 mEq NaCl per 10 cc) initiated at 1–2 cc/kg/h
b. Can coadminister intravenous furosemide to hasten correction of hyponatremia or if volume overload is a concern
4. Therapeutic target:
a. Initial goal for first 3–4 hours: increase Na by 1–2 mEq/L/h until symptoms improve or until Na has increased 6–8 mEq/L
b. Subsequent goal: Increase Na by no more than 12 mEq/L/d
5. Monitor Na every 2–3 hours

Table III. Measures to Prevent Thiazide-Induced Hyponatremia
Close monitoring of serum sodium concentration in patients receiving thiazide therapy
Counseling about the risk of excessive fluid intake
Initiation of treatment at a low dosage (eg, hydrochlorothiazide 12.5 mg daily or every 2 days)
Preventive steps in patients with borderline hyponatremia before initiation of treatment with a thiazide

the pons and elsewhere, leading to neurologic dysfunction including quadriplegia, pseudobulbar palsy, seizures, coma, and death.

CLINICAL MANAGEMENT OF TIH

The management of TIH involves the acute treatment of hyponatremia and measures to prevent recurrent hyponatremia (Table II and Table III).

Acute Management of TIH

The acute management of TIH is determined more by the presence or absence of neurologic symptoms than by the sodium level per se. Patients with acute onset of hyponatremia (decrease in sodium concentration to <120 mEq/L in <48 hours[27]) are more likely to be symptomatic and at risk for cerebral edema than those in whom hyponatremia developed more gradually.[24]

In symptomatic patients with manifestations such as lethargy or confusion or more serious manifestations such as obtundation or seizures, measures to quickly increase the serum sodium concentration are urgently needed to prevent cerebral edema. In contrast, particularly when the hyponatremia is less severe and more gradual in onset, the risk of cerebral edema is lower, and more conservative treatment is preferable.

Acute Management of Symptomatic TIH. Patients with symptomatic hyponatremia, in whom the serum sodium concentration is often <120 mEq/L, should be treated aggressively, as more thoroughly discussed in previous reviews.[12,24] Prevention of cerebral edema is paramount, and use of saline or hypertonic saline to quickly raise the serum sodium level is appropriate. The initial goal is rapid but partial correction of serum sodium concentration, to reduce the likelihood of developing cerebral edema, followed by more gradual correction, to avoid the risk of central pontine myelinosis that can accompany overly rapid correction. Complete resolution of hyponatremia can take up to a week; therefore, continued monitoring of water intake and of serum sodium concentration is needed.[28]

In symptomatic patients, the two main treatment options are infusion of either normal saline or hypertonic saline. The choice between isotonic vs hypertonic saline depends, to a large extent, on the state of the intravascular volume (ie, whether the patient is hypovolemic).[3,13] Clinical clues that suggest hypovolemia include hypotension, azotemia, and hyperuricemia. In patients with hypovolemic TIH, in whom ADH secretion stimulated by hypovolemia contributes to the inability to excrete free water, normal saline infusion is appropriate because it will restore volume and suppress ADH secretion, leading to increased free water excretion and increased serum sodium concentration.[24] If there is no increase in serum sodium after 2 hours of saline infusion, then hypertonic saline should be administered. In patients with severe manifestations such as seizures or coma, initiation of treatment with hypertonic saline to assure rapid

onset of response is recommended.[12,24] In patients with hypovolemic TIH, treating solely by restricting fluid intake would be inappropriate.

In contrast, in patients with euvolemic or hypervolemic TIH, who tend to have lower serum levels of uric acid, blood urea nitrogen, and creatinine, ADH is not a factor, and normal saline will not restore free water clearance or serum sodium concentration. Further, serum sodium concentration can actually fall if the infused sodium is excreted to a greater extent than the infused water. In such patients, hypertonic saline will predictably raise serum sodium concentration and is preferable.

Three percent NaCl (5 mEq NaCl per 10 cc) is initiated at 1 to 2 cc/kg/h with the goal of initially increasing serum sodium concentration by 1 to 2 mEq/L/h for 3 to 4 hours, aiming for a 6 to 8 mEq/L increase.[3,19,24,29] The higher dose (2 cc/kg/h) can be given to severely symptomatic patients—for example, patients with seizures or coma—and the lower dose (1 cc/kg/h) to less symptomatic patients.[29] The serum sodium level should be monitored every 2 to 3 hours.

The use of hypertonic saline should be limited to the first few hours. After the initial correction, the rate of correction should be slowed, with a goal of increasing serum sodium concentration by no more than 12 mEq/L/d (0.5 mEq/L/h), to prevent development of central pontine myelinosis.[24]

In patients with euvolemic or hypervolemic hyponatremia, administration of furosemide in addition to the hypertonic saline can increase free water clearance and thus hasten the increase of the serum sodium concentration while avoiding volume overload.[24] The more rapid increase in sodium concentration is related more to a negative water balance than to a positive sodium balance.[30] Diuresis with furosemide causes sodium loss equivalent to half of that with isotonic saline.[24] Net sodium loss due to the loop diuretic will be limited by the infused hypertonic saline, assuring that water will be excreted in excess of sodium.

The combination of hypertonic saline and furosemide has been reported to be associated with a better neurologic outcome than treatment with hypertonic saline alone.[30] However, in patients with hypovolemic hyponatremia or in whom volume status is unclear, a loop diuretic should not be administered.

It is important to bear in mind that the acute treatment of TIH can restore sodium concentration faster than intended. Free water clearance can increase rapidly due to withholding of the offending thiazide and due to suppression of ADH by saline infusion in hypovolemic patients. This underlines the need for careful monitoring of the serum sodium concentration. Tolvaptan, a V2-selective arginine vasopressin–receptor antagonist, has been shown to hasten the increase in serum sodium in patients with hyponatremia, but its role in the treatment of TIH has not been assessed.[31]

Management of Asymptomatic TIH. *Correction of Hyponatremia.* In asymptomatic or minimally symptomatic patients, serum sodium concentration tends to be less severely reduced than in patients with symptomatic hyponatremia. Stopping the offending diuretic and restricting water intake to <1 L/d is usually all that is needed. The serum sodium concentration should be increased no faster than 12 to 15 mEq/L/d, or about 0.5 mEq/L/h.[3,24] Administration of hypertonic saline is not indicated. Normal saline is not needed unless correction of volume depletion is indicated. Increasing oral salt intake in combination with fluid restriction can increase serum sodium concentration and is a logical step to take in the treatment of patients who are not hypervolemic; however, no studies have formally assessed its effect.

Although specific guidelines are lacking, clinical experience indicates that patients whose serum sodium concentration is >125 mEq/L or so and who are asymptomatic can sometimes be treated without hospital admission. This would seem appropriate assuming that the patient is reliable and can restrict fluid intake, that the physician is familiar with and comfortable with the management of mild hyponatremia, and that close follow-up can be reliably obtained. Otherwise, referral to an emergency department is preferable.

Measures to Prevent Recurrent Hyponatremia. Reviews on the management of TIH largely ignore the question of subsequent management. What measures should be taken after the hyponatremia has resolved? There are no published guidelines and virtually no studies. In this section, a clinically realistic approach is offered, based on what we know about the physiology of TIH.

Fluid Restriction. The most important intervention is *detailed* questioning about fluid intake. In patients with clearly excessive fluid intake (eg, >2.5 L/d), the patient should be instructed to reduce fluid intake to ≤1.5 L/d or so.

Sodium Intake. A very low sodium intake, often undertaken in the management of hypertension,

can contribute to the risk of developing hyponatremia by increasing the amount of water that must be excreted as free water. This is a particular concern in patients whose ability to excrete free water is reduced even before initiation of diuretic therapy. Increasing sodium intake could help, but it would seem self-defeating to instruct the hypertensive patient on a thiazide diuretic to increase sodium intake. Here, a drug other than a thiazide diuretic would be preferable.

Replacement of the Thiazide Diuretic With Another Agent. A thiazide diuretic can usually be replaced without compromising blood pressure control either with an agent other than a diuretic or, in patients who clearly require a diuretic, a loop diuretic. In treating hypertension in the elderly, calcium channel blockers are an effective alternative to diuretics and do not confer a risk of hyponatremia.

Nevertheless, in many cases, hypertension simply cannot be well controlled without a diuretic. In such cases, a loop diuretic can be prescribed, albeit with careful monitoring of serum sodium, beginning within a week or two of initiation. Similarly, in patients with borderline hyponatremia before treatment with a diuretic, use of a loop diuretic rather than a thiazide merits consideration as a cautionary measure. There are insufficient data concerning the effects on sodium of indapamide, also a nonthiazide diuretic.

Loop Diuretics. As discussed above, loop diuretics are less likely than thiazide diuretics to cause hyponatremia.[3,16–19] However, for several reasons, there is a traditional reluctance to prescribe a loop diuretic instead of a thiazide in treating essential hypertension. First, in the management of hypertension, long-term studies have not been conducted to determine whether loop diuretics prevent cardiovascular events as effectively as thiazide diuretics. Second, the diuresis caused by loop diuretics is inconvenient. Third, many physicians incorrectly assume that the powerful loop diuretics are as likely as a thiazide to cause hyponatremia. Fourth, most physicians almost automatically prescribe thiazide diuretics when treating hypertension. Finally, there are no formal studies assessing the incidence of hyponatremia in patients treated with a loop diuretic after prior documentation of TIH.

Despite these concerns, a loop diuretic is a reasonable alternative to a thiazide. Although unassessed in long-term hypertension trials, it is likely that if it controls the hypertension to the same degree, the cardiovascular protection should be substantially the same. The loop diuretic torsemide, with more reliable absorption than furosemide and a slightly longer duration of action, is reported to be more effective than furosemide and as effective as a thiazide in treating hypertension.[32,33] The problem of symptomatic diuresis can be ameliorated to some extent by varying the time of dosing to suit the convenience of the patient.

Potassium-Sparing Diuretics. Potassium-sparing diuretics also reduce free water clearance but seem less likely than a thiazide to cause hyponatremia. Combining a potassium-sparing diuretic with a thiazide could enhance the reduction in maximal dilution of urine.[16] Combining it with a loop diuretic can increase the antihypertensive effect with less risk of hyponatremia than a potassium-sparing diuretic/thiazide combination, although studies to demonstrate this have not been performed.

Dose Reduction. In general, in patients with TIH, replacement of the thiazide with a nondiuretic antihypertensive agent (or if a diuretic is needed, a loop diuretic) is the safest approach. However, sometimes a thiazide diuretic is needed. For example, a diuretic is needed in some patients to control their hypertension, but they may not tolerate a loop diuretic. In such patients, a case can be made for continuation of the thiazide at a reduced dosage in concert with avoidance of excessive fluid intake, as long as the degree of hyponatremia has been minimal (129–132 mEq/L), normalization of serum sodium concentration is documented, and careful follow-up is assured. A lower dose would increase the ability to excrete free water, would reduce the hypovolemic stimulus for ADH secretion, and can correct borderline hyponatremia in many cases.

Monitoring of Serum Sodium Concentration. Current guidelines recommend assessing serum sodium concentration within a month of initiating therapy with a thiazide diuretic. However, most cases of TIH develop within 1 to 2 weeks. It would make sense to assess serum sodium concentration within a 1 or 2 weeks of initiating treatment with a thiazide diuretic in patients older than 70 who are at higher risk for TIH. Similarly, serum sodium should be checked in elderly patients in whom the dose is being increased or who are being switched from a thiazide to the more potent chlorthalidone. The cost-effectiveness of earlier monitoring needs to be assessed.

Management of Patients With Borderline Hyponatremia. There are currently no guidelines in

place concerning management of individuals who have borderline or minimal hyponatremia (129–132 mEq/L) while taking a thiazide diuretic, a condition that might not be entirely harmless.[34] Such patients would seem to be at increased risk for developing more severe hyponatremia in the event of increased fluid intake, reduced sodium intake, intercurrent stress or illness, or addition of commonly used drugs that can affect sodium handling, such as a nonsteroidal anti-inflammatory drug. In such patients, the habitual amount of fluid intake should be ascertained, and in those with excessive intake (>1.5–2 L/d), it should be reduced. The second major issue concerns whether diuretics should be avoided. At one extreme, the not uncommon practice of many physicians of continuing thiazide diuretic therapy in such patients must be questioned, both because of the potential risk and because a nonthiazide diuretic or an antihypertensive drug other than a diuretic can usually be substituted without compromising blood pressure control. At the other extreme, the practice of many physicians of rigidly avoiding the use of all diuretics, including loop diuretics, in such patients must also be challenged, since in some cases it denies diuretic therapy to patients who truly need a diuretic. Although controlled trials are lacking, if the hypertension cannot be controlled with agents other than diuretics, a loop diuretic, with careful monitoring of serum sodium, merits consideration.

Prevention of TIH

The first step in prevention of TIH is awareness that it can happen, particularly in patients older than 70 and in women. Individuals with a high fluid intake and possibly those whose usual serum sodium concentration is in the low-normal range are likely at higher risk.

There are no guidelines regarding measures to prevent TIH. Several steps would seem reasonable, as listed in Table III. In current clinical practice, serum electrolytes are usually checked within a month of initiating diuretic therapy, mainly with an eye toward potassium levels. Recommendations ranging from a week to a month have been suggested. Since most cases of TIH develop within 1 to 2 weeks, monitoring of electrolytes within that time frame would be necessary. This would be a major departure from current practice and an inconvenience to many. Even if limited to those at high risk (age older than 70), the incidence of significant TIH might be too low to warrant checking sodium levels within this short period. The 4% incidence seen in SHEP was seen in patients taking 12.5 to 25 mg of chlorthalidone, and many cases were likely mild and asymptomatic. With low-dose hydrochlorothiazide (12.5 mg), which milligram per milligram is less potent than chlorthalidone, the incidence would be low, opening to question the cost effectiveness of monitoring serum sodium within 2 weeks.

Identifying patients with excessive fluid intake and counseling them to reduce their intake would be extremely helpful and cost-effective. However, physicians generally do not do this. An alternative approach that merits consideration would be inclusion of a warning about excessive fluid intake to accompany the filled prescription for a thiazide given to elderly patients.

Initiation of thiazide therapy at a low dosage (eg, 12.5 mg of hydrochlorothiazide either every day or every other day) would reduce the likelihood of development of TIH. As discussed above, only 10% of cases occur at this low dosage.[7] A definite recommendation by the Eighth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 8) merits consideration.

Studies have not been done to determine whether borderline hyponatremia before initiation of treatment with a thiazide increases the likelihood of developing TIH. Such patients would seem to be at increased risk; in such patients, appropriate measures to prevent TIH include either avoiding a thiazide or initiating a thiazide at a very low dosage, monitoring serum sodium values within 1 to 2 weeks, and preemptive counseling regarding fluid intake.

CONCLUSIONS

Hyponatremia is not an uncommon consequence of treatment with a thiazide diuretic among elderly patients, particularly among those with a high fluid intake. Careful monitoring of serum sodium, counseling about the risk of excessive fluid intake, and use of the lowest possible dosage are warranted in this population.

Patients with severe and symptomatic hyponatremia require urgent treatment with either saline or hypertonic saline. However, care must be taken to avoid excessively rapid restoration of serum sodium concentration. Patients with mild and asymptomatic hyponatremia can usually be treated with withdrawal of the thiazide and restriction of fluid intake.

Management of patients following restoration of a normal serum sodium concentration is discussed. Patients should be counseled to avoid excessive fluid intake, and serum sodium should be carefully monitored. In patients who truly require a diuretic, a loop diuretic is preferable to a thiazide.

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