

Diuretic-Induced Hyponatremia

Aaron Spital

University of Rochester School of Medicine, Rochester, N.Y., USA

Key Words

Hyponatremia · Diuretics · Electrolyte disorders

Abstract

Diuretics are one of the most common causes of severe hyponatremia. Yet, despite several relevant studies and years of clinical experience, the mechanism and optimal treatment of diuretic-induced hyponatremia remain unclear. What is clear is that most cases are caused by thiazide rather than loop diuretics and that severe hyponatremia can develop very rapidly in susceptible patients. In this review, I will discuss the pathogenesis, clinical features, prevention, and treatment of diuretic-induced hyponatremia in the hope that increased awareness and understanding will reduce the incidence and complications of this potentially life-threatening syndrome.

Introduction

The first detailed description of diuretic-induced hyponatremia was published over 35 years ago [1]. Since that time, numerous additional cases have been reported, and diuretics are now recognized to be one of the most important causes of severe hyponatremia [2, 3]. Yet, despite several relevant studies, the mechanism and optimal treatment of diuretic-induced hyponatremia remain unclear. In this review, I will explore the pathogenesis,

discuss the clinical features, and suggest an approach to prevention and treatment of this fascinating and potentially life-threatening syndrome.

Most cases of diuretic-induced hyponatremia are caused by thiazide or thiazidelike agents; loop diuretics are implicated much less commonly [4-6]. As discussed below, the explanation for this observation probably lies in the different effects these two classes of diuretics have on renal water and electrolyte handling. In view of these important differences, thiazide and loop diuretics will be discussed separately.

Thiazide-Induced Hyponatremia

As for all causes of hypotonic hyponatremia, one or more of the following disturbances must be responsible: (1) positive water balance; (2) negative sodium and/or potassium balance, or (3) a shift of sodium from the extracellular to the intracellular space (with osmotic inactivation). As outlined below, there is evidence that all of these may contribute to the pathogenesis of thiazide-induced hyponatremia, although the mechanism may vary from patient to patient.

Mechanisms

Positive Water Balance. The development of a positive water balance usually implies impaired renal water excretion. Is there any evidence that thiazides can do this directly? While thiazide diuretics do not inhibit concen-

trating ability, they do impair diluting ability in several ways [5, 7, 8]. First, they inhibit electrolyte transport at the cortical diluting sites, thereby raising the minimum urinary osmolality [7, 9, 10]; but while this effect reduces electrolyte free water clearance [5], it does not reduce urine flow and therefore does not directly predispose to an expansion of total body water. Second, thiazides stimulate antidiuretic hormone (ADH) release [11–13]. Third, they decrease the glomerular filtration rate acutely [9, 10, 14, 15] and increase fractional proximal water reabsorption [15], thereby reducing delivery to diluting sites. However, if these latter effects develop in response to diuretic-induced volume depletion, total body water would fall. On the other hand, if thiazides act directly to reduce distal delivery, stimulate ADH release, and/or enhance ADH action, a primary decline in urine output and an expansion of body water would be expected. While some studies support such direct effects of thiazides [4, 10, 13, 14, 16], others do not [15, 17–20]. Furthermore, no study has shown that thiazides acutely decrease urine flow.

Nevertheless, several studies suggest that total body water is expanded in some case of thiazide-induced hyponatremia. Friedman et al. [21] showed that within 6 h of ingesting a single hydrochlorothiazide-amiloride tablet, previously affected patients had a small rise in urine osmolality and a fall in serum sodium of 5.5 mmol/l in association with a small gain in weight; controls had only a slight fall in serum sodium, and their mean weight fell. Although water intake was not measured, these authors suggested that thiazides may cause polydipsia which, when combined with the renal effects of thiazides, results in an expansion of total body water and hyponatremia. Sonnenblick and Rosin [22] also found evidence of water retention in thiazide-induced hyponatremia: they showed that some patients have low serum uric acid levels and high uric acid clearances (a marker of volume expansion) which return to normal as the serum sodium concentration rises. Similarly, Abramow and Cogan [4] found that in some of their patients the fractional urea excretion was high during hyponatremia and fell with correction of the serum sodium. Furthermore, many patients with thiazide-induced hyponatremia appear euvolemic [4, 12, 23–26]. Finally, in some of them water balance was positive during the development of hyponatremia and negative during its correction [4, 17, 24, 25, 27].

If thiazides do not directly decrease urine flow, how can these observations be explained? It is important to note that most patients in whom total body water appeared expanded were drinking large quantities of water [4, 17, 24, 25, 27]. In this setting, water balance might

become positive not because of a decrease in urine flow, but rather because thiazides prevent urine output from keeping pace with a large water intake. The resulting fall in serum sodium would be magnified by concomitant electrolyte loss.

While an enlarged total body water level may contribute to the pathogenesis of some cases of thiazide-induced hyponatremia, there are many cases in which body weight fell or remained the same during the fall in serum sodium [1, 11, 23, 28, 29]. Even in the study performed by Friedman et al. [21], mild hyponatremia persisted for 24 h despite body weight falling below baseline, and 1 patient who was rechallenged developed mild hyponatremia with no change in weight. Fichman et al. [23] measured total body water in some of their patients and found the mean to be normal. In these cases, other explanations for hyponatremia must be sought.

Negative Electrolyte Balance. There is much evidence that patients with thiazide-induced hyponatremia are electrolyte deficient. First, virtually all relevant studies have found that during the development of this syndrome, cation balance is negative [1, 4, 17, 23, 24, 28, 29]. Second, once diuretics are withdrawn, urinary sodium excretion falls to very low levels [1, 23, 30]. Third, many of these patients are hypokalemic [1, 4, 17, 23, 24, 30, 31]. Finally, a few of them present with clear evidence of volume depletion [4, 32].

Cation depletion alone would not be expected to cause marked hyponatremia because water excretion normally increases as the serum sodium concentration falls. However, because thiazides interfere with renal water excretion, they impair this normal osmoregulatory response. Thus, as in most patients with hyponatremia, urine osmolality is inappropriately high relative to the osmolality of plasma and often exceeds it [1, 4, 12, 17, 22, 23, 25, 28]. In fact, rejected cations may sometimes be excreted at a total concentration which exceeds that of plasma [17]. In this unusual situation, hypertonic urinary losses could directly lower the plasma sodium level, even in the absence of water intake.

Diuretic-induced volume depletion probably contributes to the genesis of this syndrome in some cases. Hypovolemia may stimulate the release of ADH which is elevated in many of these patients [4, 12, 13, 25], though not in all [17, 21]. As previously noted, volume depletion may also impair renal water excretion by decreasing the glomerular filtration rate and increasing proximal reabsorption, thereby reducing distal delivery [15, 18, 33]; this can cause water retention even in the absence of ADH [34]. Supporting the importance of volume depletion is the

observation that the urine osmolality often falls after sodium repletion [1, 23]. However, since it takes time to develop volume depletion, this probably does not contribute to the very rapid falls in serum sodium which are sometimes seen within hours of beginning thiazide therapy.

For reasons which are unclear, after thiazides have been administered for several days, there is an increase in inner medullary interstitial osmolality which may also contribute to the antidiuretic effect of these drugs [33].

Fichman et al. [23] emphasized the importance of potassium depletion in diuretic-induced hyponatremia. The great majority of their 25 patients were hypokalemic, and hyponatremia was corrected in 4 of them by potassium repletion despite continued diuretic use and sodium restriction. These investigators argued that potassium depletion predisposes to hyponatremia because the serum sodium concentration is dependent upon the ratio of the sum of exchangeable sodium and potassium to total body water. They also speculated that potassium depletion causes a shift of sodium to the intracellular space, thereby further compromising the extracellular volume and stimulating ADH release.

While potassium depletion likely contributes to the genesis of hyponatremia in many cases, it is not essential. Indeed, hyponatremia has developed in some patients taking potassium-sparing diuretics in the absence of hypokalemia [1, 4, 6, 35]. In a careful study of one of these patients [1], spironolactone induced hyponatremia despite positive potassium balance. Furthermore, when only potassium (but not sodium) stores are depleted, patients remain at risk of recurrence of hyponatremia if water intake increases [4, 36].

One of the surprising features of thiazide-induced hyponatremia is that, despite a negative cation balance, many patients appear to be euvolemic [4, 12, 23–26]. The explanation for this seeming paradox may be that enough water is retained to offset the initial tendency toward hypovolemia [4, 23]. In a sense, hyponatremia is the price paid to preserve the extracellular volume. If this is true, why is it that other patients who develop hyponatremia as a result of electrolyte loss (e.g., from the gastrointestinal tract) are typically hypovolemic? One possibility is that the mean water intake may be higher in patients whose hyponatremia is caused by thiazides. There is evidence that water intake is maintained or increased in many patients with thiazide-induced hyponatremia [4, 17, 21, 24]. Stimulation of water intake would not only help defend the extracellular volume, but would also explain why thiazides are one of the most common causes of severe hyponatremia.

Transcellular Sodium Shift. While changes in external salt and water balance are probably responsible for most episodes of thiazide-induced hyponatremia [4, 17], in a careful case study Fuisz et al. [1] found that changes in external sodium and water balance did not completely account for the fall in serum sodium. Furthermore, chlorothiazide induced hyponatremia in their patient despite sodium supplementation and positive sodium balance. These observations led the authors to conclude that a shift of sodium to the intracellular space contributed to the pathogenesis of hyponatremia. In another case study, Johnson and Wright [29] also concluded that external cation and water balances did not fully explain the fall in serum sodium; these authors speculated that sodium entered cells and became osmotically inactive. If a transcellular sodium shift does occur in this syndrome, magnesium depletion may contribute by reducing cell membrane adenosine triphosphatase activity [37].

Synthesis. Despite many studies on thiazide-induced hyponatremia, the pathogenesis of this intriguing syndrome remains unclear. The available evidence suggests that the mechanism of hyponatremia may vary from case to case. However, it is likely that all affected patients have reduced body stores of sodium (and usually potassium) and a reversibly impaired ability to excrete water. In some cases, diuretic-induced electrolyte loss appears to be the primary disturbance with water retention occurring secondarily; in these patients total body water may be low or nearly normal, depending upon the level of water intake. In other patients, total body water may actually be increased as a result of direct inhibitory effects of thiazides upon urinary dilution combined with a large water intake; this, along with a reduction in electrolyte stores, leads to hyponatremia. While changes in external salt and water balance probably account for hyponatremia in most cases, a shift of sodium from the extracellular to the intracellular space may play a role in some patients.

Clinical Characteristics

Most cases of thiazide-induced hyponatremia have occurred in elderly small women who have been prescribed diuretics for the treatment of hypertension [2–4, 6, 11, 17, 21, 23, 31, 32]. At least two factors probably account for this group's predisposition to hyponatremia: First, because of their small size, small changes in body water and electrolyte content can lead to marked changes in serum sodium. Second, healthy elderly people do not excrete water as efficiently as do younger ones, especially those who have previously experienced thiazide-induced hyponatremia [11]. Furthermore, while thiazides impair

diluting ability in people of all ages, this effect is more pronounced in the elderly [11].

One of the most remarkable features of thiazide-induced hyponatremia is the rapidity with which it can occur. In susceptible individuals, the serum sodium may fall within hours of diuretic ingestion, and severe hyponatremia can develop within less than 2 days [1, 4, 17, 21, 23, 24, 29]. In most reported cases the duration of thiazide use had been less than 2 weeks. On the other hand, in some cases thiazides had been used chronically without incident until, for some reason, water intake increased [27].

While some patients are volume depleted on presentation, most appear to be euvolemic [3, 4, 12, 22–26]. Serum levels of creatinine, blood urea nitrogen, and uric acid are often normal and sometimes low. These findings are also typical of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). Fichman et al. [23] suggested that the serum potassium and bicarbonate concentrations may be useful differential points. However, while most patients with thiazide-induced hyponatremia are hypokalemic, those who have taken potassium-sparing diuretics are often not [1, 4, 6, 35]. Furthermore, even among patients using thiazide type agents alone, there is considerable overlap of their serum potassium and bicarbonate concentrations with those of patients with SIADH [23]. However, the lower the serum potassium and the higher the serum bicarbonate, blood urea nitrogen, creatinine, and uric acid, the more likely it is that diuretics are responsible for hyponatremia.

Whether or not patients are symptomatic depends on the rate and magnitude of the fall in serum sodium. As for all causes of hyponatremia, symptoms result primarily from cerebral dysfunction and may include lethargy, confusion, dysarthria, agitation, seizures, stupor, and coma.

Treatment, Prognosis, and Prevention

Appropriate treatment of thiazide-induced hyponatremia includes stopping the diuretic, restricting water, and repleting electrolyte stores (including magnesium). How aggressive therapy should be depends upon the symptomatology and duration of hyponatremia [6, 38]. In asymptomatic patients, water restriction and a regular diet (usually supplemented with potassium) provide safe and effective therapy.

In patients with mild symptoms (e.g., lethargy, confusion) electrolytes should be given intravenously, but rapid increases in serum sodium should be avoided [6, 39]. When hyponatremia develops over several days, as is often the case when thiazides are responsible, there is an

adaptive loss of brain solute which protects against cerebral edema [38, 39]. As hyponatremia is corrected, this lost solute is recovered, but this process takes time. Therefore, rapid correction of chronic hyponatremia dehydrates the brain which can cause 'osmotic demyelination' in the central pons and elsewhere. These lesions may result in severe and sometimes irreversible neurological deficits [39]. Hypokalemia, which is common in these patients, may magnify the risk of this serious complication [40]. To prevent rapid increases in the serum sodium concentration, hypertonic solutions should be avoided. In the usual hypokalemic patient, a rational approach is to infuse a solution of 0.45% NaCl containing about 50 mmol/l of KCl (total cation concentration 127 mEq/l) at a rate calculated to raise the serum sodium by no more than 0.5 mEq/l/h [3, 39], although some experts recommend a faster rate of correction [38]. The total cation deficit can be estimated by multiplying the reduction in serum sodium times total body water [41]. Subtracting the estimated potassium deficit from this total yields the approximate sodium deficit.

It is important to realize that as electrolyte stores are repleted, ADH levels will fall and renal water excretion may increase markedly, resulting in unexpectedly large increases in the serum sodium [39]. Therefore, during therapy it is important to monitor serum electrolytes and urine output frequently. If the serum sodium or urine output rapidly increases, electrolyte supplementation should be stopped. Under these circumstances, it may even be necessary to partially replace water losses in order to slow the rate of correction and reduce the risk of osmotic brain injury.

Hypertonic saline should be reserved for patients with symptoms indicative of life-threatening cerebral edema (e.g., agitation, seizures, coma). In these unusual cases, 3% NaCl should be administered at a rate of about 2 ml/kg/h which will increase the serum sodium by about 2 mEq/l/h [6, 38, 39]. This infusion should be continued for about 3–4 h, until the serum sodium has increased by 6–8 mEq/l and symptoms have abated. At this point further treatment should follow the guidelines recommended for less severe cases. Obviously, close follow-up is essential and is best accomplished in an intensive care setting.

Once the serum sodium has been corrected, water intake should be liberalized. However, the serum sodium should continue to be followed closely, since these patients may be at risk of recurrent hyponatremia for at least one week after diuretic therapy has been stopped [36].

When recognized quickly and treated appropriately the prognosis of thiazide-induced hyponatremia is very

good, even when severe [3]. Most of these patients recover completely. Neurological complications appear to result from osmotic demyelination secondary to rapid and/or excessive correction of hyponatremia or less commonly from cerebral edema in cases in whom the serum sodium has fallen precipitously [3, 38, 39]. The mortality rate is less than 10%; most deaths are probably not due to hyponatremia per se but rather to the underlying disease [3, 42].

How can this syndrome be prevented? When prescribing thiazides, low doses should be used, and initially the serum sodium concentration should be monitored closely, particularly in patients at risk. These include those who are elderly, female, or small; those who ingest little salt or lots of water; and those who have other risk factors for hyponatremia [43]. In these susceptible people, the serum sodium concentration may fall precipitously; therefore, it should be measured within one day after beginning therapy. If the serum sodium level falls more than a few milliequivalents per liter, the diuretic should be stopped. If there has been little or no change in the serum sodium, it should be rechecked 1–2 days later to be sure the level is stable. Even patients who have done well on chronic thiazide therapy may develop severe hyponatremia if water intake increases [27]. Therefore, all patients using these drugs should be educated about the danger of excessive drinking, and the serum sodium concentration should be followed carefully whenever an increase in water intake is prescribed (e.g., to prevent recurrent nephrolithiasis).

Hyponatremia Caused by Loop Diuretics

Loop diuretics appear to cause hyponatremia much less frequently than do thiazides [5, 6, 38]. At least two factors may account for this observation. First, because loop diuretics inhibit electrolyte transport in the thick ascending limb, they reduce the osmolality of the medullary interstitium. Therefore, in contrast to thiazides, they inhibit concentrating as well as diluting ability [5, 7, 38]. In fact, loop diuretics have been used successfully to increase water excretion and correct hyponatremia in edematous states and SIADH [8, 44, 45]. Second, in contrast to thiazides, these powerful diuretics have a short duration of action; therefore, they induce brief bursts of electrolyte excretion. This is followed by avid electrolyte retention during which time depleted electrolyte stores may be replenished [46]. Therefore, the likelihood of sustained electrolyte depletion may paradoxically be less with loop diuretics than with thiazides.

Despite these considerations, cases of severe hyponatremia secondary to loop diuretics have been described [6, 22, 26, 47]. There are several differences in presentation as compared with thiazide-induced hyponatremia: the indication is more often heart failure than hypertension [6], the duration of therapy is usually longer [6, 22], and the serum blood urea nitrogen and uric acid levels tend to be higher [22]. In some of these cases it is likely that diuretic-induced volume depletion reduces the ability to excrete water by the mechanisms previously discussed [19, 47]. In other cases, water excretion may be impaired by the underlying disease (e.g., heart failure). Under these circumstances, if electrolyte intake is low and water intake maintained, diuretics will cause a reduction in body electrolyte stores, a proportionately smaller reduction in total body water, and, therefore, a fall in serum sodium.

While hyponatremia induced by loop diuretics has not been carefully studied, it is likely that the risk factors are similar to those for thiazide-induced hyponatremia. Therefore, serum electrolytes should be measured soon after beginning loop diuretics in small elderly people and in those with habitually large fluid intakes, especially if their electrolyte intake is low (e.g., beer drinkers).

Treatment of hyponatremia caused by these agents in nonedematous patients is similar to that recommended for thiazide-induced hyponatremia. However, it is important to resist the temptation to stop loop diuretics when hyponatremia develops in patients with heart failure (or other major edema-forming states). In these patients, induction of a negative salt and water balance is essential, and loop diuretics may actually increase water excretion [8, 45]. Appropriate therapy includes water restriction and sometimes angiotensin-converting enzyme inhibitors [38, 48].

References

- 1 Fuisz RE, Lauler DP, Cohen P: Diuretic-induced hyponatremia and sustained antidiuresis. *Am J Med* 1962;33:783-791.
- 2 Booker JA: Severe symptomatic hyponatremia in elderly outpatients: The role of thiazide therapy and stress. *J Am Geriatr Soc* 1984;32:108-113.
- 3 Sterns RH: Severe symptomatic hyponatremia: Treatment and outcome. A study of 64 cases. *Ann Intern Med* 1987;107:656-664.
- 4 Abramow M, Cogan E: Clinical aspects and pathophysiology of diuretic-induced hyponatremia. *Adv Nephrol Necker Hosp* 1984;13:1-28.
- 5 Rose BD: New approach to disturbances in the plasma sodium concentration. *Am J Med* 1986;81:1033-1040.
- 6 Sonnenblick M, Friedlander Y, Rosin AJ: Diuretic-induced severe hyponatremia: Review and analysis of 129 reported patients. *Chest* 1993;103:601-606.
- 7 Seldin DW, Eknoyan G, Suki WN, Rector FC: Localization of diuretic action from the pattern of water and electrolyte excretion. *Ann NY Acad Sci* 1966;139:328-343.
- 8 Szatalowicz VL, Miller PD, Lacher JW, Gordon JA, Schrier RW: Comparative effect of diuretics on renal water excretion in hyponatremic oedematous disorders. *Clin Sci* 1982;62:235-238.
- 9 Earley LE, Kahn M, Orloff J: The effects of infusions of chlorothiazide on urinary dilution and concentration in the dog. *J Clin Invest* 1961;40:857-866.
- 10 Heinemann HO, Demartini FE, Laragh JH: The effect of chlorothiazide on renal excretion of electrolytes and free water. *Am J Med* 1959;26:853-861.
- 11 Clark BA, Shannon RP, Rosa RM, Epstein FH: Increased susceptibility to thiazide-induced hyponatremia in the elderly. *J Am Soc Nephrol* 1994;5:1106-1111.
- 12 Ghose RR: Plasma arginine vasopressin in hyponatremic patients receiving diuretics. *Postgrad Med J* 1985;61:1043-1046.
- 13 Sonnenblick M, Algur N, Rosin A: Thiazide-induced hyponatremia and vasopressin release. *Ann Intern Med* 1989;110:751.
- 14 Januszewicz W, Heinemann HO, Demartini FE, Laragh JH: A clinical study of the effects of hydrochlorothiazide on the renal excretion of electrolytes and free water. *N Engl J Med* 1959;261:264-269.
- 15 Walter SJ, Laycock JF, Shirley DG: A micro-puncture study of proximal tubular function after acute hydrochlorothiazide administration to Brattleboro rats with diabetes insipidus. *Clin Sci* 1979;57:427-434.
- 16 Abramow M, Dratwa M: Interaction of vasopressin and diuretics on the isolated rabbit collecting tubule. *Eur J Clin Invest* 1974;4:353.
- 17 Ashraf N, Locksley R, Arief AI: Thiazide-induced hyponatremia associated with death or neurologic damage in outpatients. *Am J Med* 1981;70:1163-1168.
- 18 Earley LE, Orloff J: The mechanism of antidiuresis associated with the administration of hydrochlorothiazide to patients with vasopressin-resistant diabetes insipidus. *J Clin Invest* 1962;41:1988-1997.
- 19 Pena JC, Ruiz F, Abraham J: Impaired water excretion following diuretic therapy. *Clin Pharmacol Ther* 1968;10:110-117.
- 20 Urakabe S, Shirai D, Yuasa S, Kimura G, Orita Y, Abe H: Comparative study of the effects of different diuretics on the permeability properties of the toad bladder. *Comp Biochem Physiol [C]* 1976;53:115-119.
- 21 Friedman E, Shadel M, Halkin H, Farfel Z: Thiazide-induced hyponatremia: Reproducibility by single dose challenge and an analysis of pathogenesis. *Ann Intern Med* 1989;110:24-30.
- 22 Sonnenblick M, Rosin AJ: Significance of the measurement of uric acid fractional clearance in diuretic induced hyponatremia. *Postgrad Med J* 1986;62:449-452.
- 23 Fichman MP, Vorherr H, Kleeman CR, Telfer N: Diuretic-induced hyponatremia. *Ann Intern Med* 1971;75:853-863.
- 24 Kennedy RM, Earley LE: Profound hyponatremia resulting from a thiazide-induced decrease in urinary diluting capacity in a patient with primary polydipsia. *N Engl J Med* 1970;282:1185-1186.
- 25 Luboshitzky R, Tal-Or Z, Barzilai D: Chlorothalidone-induced syndrome of inappropriate secretion of antidiuretic hormone. *J Clin Pharmacol* 1978;18:336-339.
- 26 Roberts CJC, Mitchell JV, Donley AJ: Hyponatremia: Adverse effect of diuretic treatment. *Br Med J* 1977;i:210.
- 27 Kone B, Gimenez L, Watson AJ: Thiazide-induced hyponatremia. *South Med J* 1986;79:1456-1457.
- 28 Horowitz J, Keynan A, Ben-Ishay D: A syndrome of inappropriate ADH secretion induced by cyclothiazide. *J Clin Pharmacol* 1972;12:337-341.
- 29 Johnson JE, Wright LF: Thiazide-induced hyponatremia. *South Med J* 1983;76:1363-1367.
- 30 Beresford HR: Polydipsia, hydrochlorothiazide, and water intoxication. *JAMA* 1970;214:879-883.
- 31 Pinnock CA: Hyponatremia associated with hydrochlorothiazide treatment. *Br Med J* 1978;i:48.
- 32 Ashouri O: Severe diuretic-induced hyponatremia in the elderly. *Arch Intern Med* 1986;146:1355-1357.
- 33 Shirley DG, Walter SJ, Laycock JF: The antidiuretic effect of chronic hydrochlorothiazide treatment in rats with diabetes insipidus: Renal mechanisms. *Clin Sci* 1982;63:533-538.
- 34 Harrington AR: Hyponatremia due to sodium depletion in the absence of vasopressin. *Am J Physiol* 1972;222:768-774.
- 35 Tarssanen L, Huikko M, Rossi M: Amiloride-induced hyponatremia. *Acta Med Scand* 1980;208:491-494.
- 36 Hamburger S, Koprivica B, Ellerbeck E, Covinsky JO: Thiazide-induced syndrome of inappropriate secretion of antidiuretic hormone: Time course of resolution. *JAMA* 1981;246:1235-1236.
- 37 Dyckner T, Wester PO: Effects of magnesium infusions in diuretic induced hyponatremia. *Lancet* 1981;i:585-586.
- 38 Kumar S, Berl T: Sodium. *Lancet* 1998;352:220-228.
- 39 Sterns RH, Spital A, Clark EC: Disorders of water balance; in Kokko JP, Tannen RL (eds): *Fluids and Electrolytes*. Philadelphia, Saunders, 1996, pp 63-109.
- 40 Lohr JW: Osmotic demyelination syndrome following correction of hyponatremia: Association with hypokalemia. *Am J Med* 1994;96:408-413.
- 41 Spital A, Sterns RH: The paradox of sodium's volume of distribution: Why an extracellular solute appears to distribute over total body water. *Arch Intern Med* 1989;149:1255-1257.
- 42 Hochman I, Cabili S, Peer G: Hyponatremia in internal medicine ward patients: Causes, treatment and prognosis. *Isr J Med Sci* 1989;25:73-76.
- 43 Grantham JJ, Brown RW, Schloerb PR: Asymptomatic hyponatremia and bronchogenic carcinoma: The deleterious effects of diuretics. *Am J Med Sci* 1965;62:274-279.
- 44 Decaux G, Waterlot Y, Genette F, Mockel J: Treatment of the syndrome of inappropriate secretion of antidiuretic hormone with furosemide. *N Engl J Med* 1981;304:329-330.
- 45 Schrier RW, Lehman D, Zacherle B, Earley LE: Effect of furosemide on free water excretion in edematous patients with hyponatremia. *Kidney Int* 1973;3:30-34.
- 46 Wilcox CS, Guzman NJ, Mitch WE, et al: Na⁺, K⁺, and BP homeostasis in man during furosemide: Effects of prazosin and captopril. *Kidney Int* 1987;31:135-141.
- 47 DeRubeis FR, Michelis MF, Beck N, Davis BB: Complications of diuretic therapy: Severe alkalosis and syndrome resembling inappropriate secretion of antidiuretic hormone. *Metabolism* 1970;19:709-719.
- 48 Packer M, Medina N, Yushak M: Correction of dilutional hyponatremia in severe chronic heart failure by converting-enzyme inhibition. *Ann Intern Med* 1984;100:782-789.