

NARRATIVE REVIEW

A Review of Drug-Induced Hyponatremia

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Hyponatremia (defined as a serum sodium level < 134 mmol/L) is the most common electrolyte abnormality in hospitalized patients. Certain drugs (eg, diuretics, antidepressants, and antiepileptics) have been implicated as established causes of either asymptomatic or symptomatic hyponatremia. However, hyponatremia occasionally may develop in the course of treatment with drugs used in everyday clinical practice (eg, newer antihypertensive agents, antibiotics, and proton pump inhibitors). Physicians may not always give proper attention in time to undesirable drug-induced hyponatremia. Effective clinical management can be handled through awareness of the adverse effect of certain pharmaceutical compounds on serum sodium levels. Here, we review clinical information about the incidence of hyponatremia associated with specific drug treatment and discuss the underlying pathophysiological mechanisms.

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INDEX WORDS: Adverse drug reaction; hyponatremia; sodium homeostasis; syndrome of inappropriate secretion of antidiuretic hormone; water homeostasis.

H yponatremia (defined as a serum sodium level < 134 mmol/L) is a common electrolyte disturbance in clinical practice that is associated with considerable morbidity and mortality.^{1,2} Drugs are a common cause of electrolyte abnormalities, and a careful drug history is essential in patients with electrolyte abnormalities. One of the more common electrolyte abnormalities that may be drug induced is hyponatremia. A thorough understanding of the pathophysiological process of drug-induced hyponatremia and associated risk factors is of great importance for prevention and prompt and effective intervention in this potentially life-threatening disturbance.

Here, we review clinical information about the incidence of hyponatremia associated with specific drug treatment and discuss the underlying pathophysiological mechanisms and therapeutic implications.

PATHOGENETIC ASPECTS OF HYPONATREMIA

Hyponatremia is ascribed to either water retention or (less often) loss of effective solute (sodium plus potassium) in excess of water. Because the capacity for water excretion normally is so great, retention of water resulting in hyponatremia takes place only in the presence of conditions that impair renal excretion of water. An exception to this rule is primary polydipsia, in which the excessive water intake can overwhelm even normal excretory capacity. Given that suppression of arginine vasopressin (antidiuretic hormone [ADH]) secretion is essential for the excretion of any water load, the presence of high serum ADH concentrations is the sine qua non for the development and maintenance of hyponatremia. Virtually all causes of hyponatremia (except renal failure and primary polydipsia) are characterized by an excess of ADH (despite the presence of hypotonicity), most frequently caused by syndrome of inappropriate ADH secretion (SIADH) or effective circulating volume depletion (which is a normal stimulus to ADH secretion).^{1,3}

A decrease in serum sodium concentration creates an osmotic gradient between extracellular and intracellular fluid in brain cells, causing movement of water into cells. Therefore, symptoms of hyponatremia (predominantly neurological) are attributed to cerebral edema. Moreover, they are related to both the severity and rapidity

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of decrease in serum sodium levels.^{2,4-6} Hyponatremic patients at risk of neurological complications caused by acute cerebral edema are postoperative menstruating women, elderly women on thiazide therapy, children, psychiatric polydipsic patients, and hypoxemic patients.⁷

DRUG-INDUCED HYPONATREMIA

Hyponatremia related to drug treatment can be caused by dozens, perhaps hundreds, of medications. Because hyponatremia can have many

Table 1. Principal Causes and Underlying Mechanisms of Drug-Induced Hyponatremia

Drugs affecting sodium and water homeostasis
Diuretics
Thiazides ⁸⁻¹⁸
Indapamide ¹⁹
Amiloride
Loop diuretics ^{8,14}
Drugs affecting water homeostasis
Increased hypothalamic production of ADH
Antidepressants
Tricyclic antidepressants (amitriptyline, protriptyline, desipramine) ²⁰
Selective serotonin reuptake inhibitors ²¹⁻²⁵
Monoamine oxidase inhibitors ²⁶
Antipsychotic drugs
Phenothiazines (thioridazine, trifluoperazine) ^{27,28}
Butyrophenones (haloperidol) ²⁹
Antiepileptic drugs
Carbamazepine, ³⁰⁻³⁵ oxcarbazepine, ^{33,36,37} sodium valproate ³⁸
Anticancer agents
Vinca alkaloids (vincristine, vinblastine) ³⁹⁻⁴²
Platinum compounds (cisplatin, carboplatin) ⁴²⁻⁴⁴
Alkylating agents (intravenous cyclophosphamide, ⁴⁵⁻⁴⁷ melphalan, ⁴⁸ ifosfamide ⁴⁹)
Miscellaneous (methotrexate, interferon α and γ , levamisole, pentostatin, monoclonal antibodies) ^{42,50}
Opiates ⁵¹
Potentiation of ADH effect
Antiepileptic drugs
Carbamazepine, ³⁰⁻³³ lamotrigine ⁵²
Antidiabetic drugs
Chlorpropamide, ⁵³⁻⁵⁵ tolbutamide ⁵⁶
Anticancer agents
Alkylating agents (intravenous cyclophosphamide) ⁴⁶
Nonsteroidal anti-inflammatory drugs ⁵⁷⁻⁶⁰
Reset osmostat
Antidepressants
Venlafaxine ⁶¹
Antiepileptic drugs
Carbamazepine ³³

Abbreviation: ADH, antidiuretic hormone.

Table 2. Rare Causes of Drug-Induced Hyponatremia

Antihypertensive agents
Angiotensin-converting enzyme inhibitors ⁶²
Amlodipine ⁶³
Immune globulin (intravenous) ^{64,65}
3,4-Methylenedioxymethylamphetamine (ecstasy) ^{66,67}
Antibiotics
Trimethoprim-sulfamethoxazole, ⁶⁸ ciprofloxacin, ⁶⁹ cefoperazone/sulbactam, ⁷⁰ rifabutin ⁷¹
Antiarrhythmic
Amiodarone, ⁷² lorcaïnide, ⁷³ propafenone ⁷⁴
Theophylline ⁷⁵
Proton pump inhibitors ⁷⁶
Bromocriptine ⁷⁷
Terlipressin ⁷⁸
Duloxetine ⁷⁹
Fluorescein angiography ⁸⁰
Bupropion ⁸¹

other causes, the diagnosis of drug-induced hyponatremia can easily be overlooked.

As shown in evidence from small studies and case reports, drugs may cause hyponatremia by affecting sodium homeostasis and water homeostasis. Clinical information about the incidence and pathophysiological process of hyponatremia of the most commonly offending agents is presented first (Table 1). Rarer causes derived from occasionally reported cases also are presented (Table 2).

Drugs Affecting Sodium and Water Homeostasis

Diuretic Treatment

Diuretics make up one of the most common causes of hyponatremia, with an estimated incidence of 11% in 1 series of 114 geriatric patients.^{8,9} Interestingly, we recently showed that diuretics are the most common cause of community-developed hyponatremia.¹⁰ Diuretic-induced hyponatremia is caused almost exclusively by thiazide or thiazide-like agents.^{8,11-17} Loop diuretics, by inhibiting sodium chloride reabsorption in the thick ascending limb of the loop of Henle, reduce the osmolarity of the medullary interstitium. Consequently, loop diuretics rarely are associated with hyponatremia because they impair both the renal concentrating and diluting mechanisms.^{8,14} Conversely, thiazide diuretics acting solely in the distal tubules do not interfere with urinary concentration and the ability of ADH to promote water retention, which is the critical point for the development of hyponatremia.

It should be noted that hyponatremia also follows indapamide administration, as well as the combination of hydrochlorothiazide and amiloride.^{19,82} The combination of hydrochlorothiazide and amiloride appears to increase the risk of hyponatremia. This increase probably is caused by the additional effect of amiloride on the renal handling of sodium. Amiloride has a direct effect on the collecting tubule, increasing sodium loss. Effects of thiazides are mainly on the distal tubule; therefore, the combination compounds the urinary loss of sodium. Moreover, amiloride, which spares potassium, aggravates thiazide-induced hyponatremia as a consequence of potassium retention by exchanging it for sodium in the distal tubule. Thus, sodium deficiency has been implicated as the major etiologic factor of hyponatremia induced by the combination of amiloride plus thiazide.⁸²

Despite numerous studies, the pathophysiological mechanisms underlying diuretic-induced hyponatremia are unclear. Among the implicated mechanisms, the most important are as follows: (1) excess renal loss of effective solutes (potassium plus sodium) compared with water losses resulting from both diuretic-induced electrolyte losses and ADH-induced water retention; (2) diuretic-induced volume depletion that appropriately stimulates ADH secretion; (3) the coexistent hypokalemia leading to a transcellular cation exchange in which potassium leaves the cells to replenish the extracellular stores, whereas sodium moves into cells to preserve electroneutrality; (4) direct inhibition of urinary dilution by diminishing sodium chloride reabsorption in the renal tubules; (5) stimulation of thirst; (6) magnesium depletion; and (7) excessive ADH secretion.^{8,11-18} Furthermore, acute severe hyponatremia occasionally is observed as an idiosyncratic reaction, particularly in subjects who consume large quantities of water.¹¹ Most cases of thiazide-induced hyponatremia occur in elderly patients, with a female predominance.^{8,13,16} Furthermore, subjects with low body mass appear to be more prone to this complication.⁸

There are 2 groups of patients with diuretic-induced hyponatremia, one consistent with extracellular volume depletion and another that simulates SIADH. Serum uric acid level has been proposed as an index to discriminate between these 2 pathophysiological constructs.^{83,84} Re-

cently, we validated this concept, and serum uric acid levels that could differentiate the 2 subgroups of diuretic-induced hyponatremia also were defined.¹⁰ Specifically, patients with a serum uric acid level less than 4 mg/dL ($<238 \mu\text{mol/L}$) showed a biochemical profile consistent with an SIADH-like state, whereas patients with a serum uric acid level of 4 mg/dL or greater had a biochemical profile compatible with extracellular volume depletion. Recognition of these 2 profiles aids the evaluation and management of patients. In patients with extracellular volume depletion, normal saline solution with or without potassium chloride should be administered intravenously to correct hypovolemia and hypokalemia, if present. Conversely, in patients with an SIADH-like state who present with severe symptomatic hyponatremia, the treatment consists of hypertonic sodium chloride solution (3%) administration, along with water restriction.

The diagnosis of diuretic-induced hyponatremia is based on a history of diuretic use and the finding that hyponatremia resolved after discontinuing the offending agent. However, achievement of normonatremia and full recovery of diluting ability may be delayed for 1 to 2 weeks after drug withdrawal. Consequently, in patients with diuretic-induced hyponatremia and an SIADH-like profile, unless there is strong evidence to suggest an underlying cause for SIADH, a comprehensive diagnostic evaluation should be postponed for 2 to 3 weeks. However, taking into consideration that thiazides may aggravate the hyponatremia induced by SIADH, an evaluation is a prudent approach if even mild hyponatremia persists after this diagnostic waiting period.

Drugs Affecting Water Homeostasis

Except for diuretics, several other drugs that impair the renal diluting capacity also can induce hyponatremia (Table 1). There are 3 possible ways drugs can affect water homeostasis: they can increase ADH secretion centrally, potentiate the effect of endogenous ADH at the renal medulla, and reset the osmostat, thus lowering the threshold for ADH secretion (Table 1). Several of the most important offending agents are reviewed here.

Drugs that Increase ADH Secretion Centrally

Psychotropic agents. Psychotropic agents have often been implicated in the cause of hyponatremia, including both antidepressants (tricyclics, selective serotonin reuptake inhibitors [SSRIs], and monoamine oxidase inhibitors) and antipsychotic drugs (phenothiazines and butyrophenones).²⁰⁻²⁹

The mechanism by which these drugs cause hyponatremia is believed to be the development of SIADH. However, it should be emphasized that low serum sodium levels in emotionally disturbed or psychotic patients may not be a direct consequence of these medications. Among the most frequent causes of hyponatremia in this population are the underlying psychosis itself⁸⁵ and the compulsive water drinking. Primary polydipsia is prominent in patients with psychosis, affecting nearly 7% of patients with schizophrenia.^{86,87} In addition to the underlying psychosis, the sensation of a dry mouth caused by psychotropic drugs (especially phenothiazines) may contribute to the increase in water intake.²⁸ Thus, causality between psychotropic agents and hyponatremia was shown more persuasively with antidepressants and mainly with SSRIs, which cause hyponatremia more frequently than other antidepressant drugs. The incidence of hyponatremia caused by SSRIs varies widely from 0.5% to 32%. In the majority of cases, hyponatremia occurs within the first few weeks of the onset of therapy, whereas the normonatremia is achieved within 2 weeks after drug withdrawal. Older age and concomitant use of diuretics are the most important risk factors for the development of hyponatremia associated with SSRIs.²³⁻²⁵

Antiepileptics. Hyponatremia has repeatedly been associated with carbamazepine therapy.³⁰⁻³⁵ Carbamazepine can induce hyponatremia by increasing ADH release from the neurohypophysis. The incidence of carbamazepine-induced hyponatremia ranged widely from 4.8% to 41.5%, depending on the patient population studied.³³⁻³⁵ Specifically, this electrolyte disturbance frequently was encountered in the elderly or subjects who simultaneously used other medications known to cause hyponatremia (mainly diuretics).³³⁻³⁵ It is noteworthy that the hyponatremic effects of carbamazepine correlated with carbamazepine dose, serum carbamazepine level, and lower initial serum sodium concentration.³³⁻³⁵

Oxcarbazepine is a 10-keto analogue of carbamazepine and is a useful drug in treating patients with the same seizure types, but it may have an improved toxicity profile. However, the prevalence of hyponatremia, as well as the frequency of severe hyponatremia, is greater in patients treated with oxcarbazepine than with carbamazepine.^{33,36,37} Finally, valproic acid can cause hyponatremia, possibly because of SIADH.³⁹

Antineoplastic agents. Vincristine and, less often, vinblastine are associated with hyponatremia.³⁹⁻⁴² These drugs alter the normal osmoreceptor control of ADH secretion through a direct toxic effect on the neurohypophysis and hypothalamic system. That peripheral neuropathy often is observed in patients with vinca alkaloid-related SIADH is indirect evidence for this neurological toxicity.³⁹

Hyponatremia associated with platinum compounds is described more frequently with cisplatin than with carboplatin.^{42,43} The possible underlying pathophysiological mechanisms by which cisplatin induces hyponatremia are SIADH and renal salt wasting.⁴⁴ Cisplatin-induced hyponatremia often is combined with hypomagnesemia, hypokalemia, and hypocalcemia, with increased magnesium, potassium, and calcium renal losses, respectively. This constellation of electrolyte disturbances (observed only rarely in patients with SIADH) is believed to be mediated by cisplatin-related tubular necrosis. The incidence of hyponatremia secondary to cisplatin can be as high as 43%. However, it is difficult to define precisely given that the majority of cases described are in case reports.^{42,43}

Another drug that deserves emphasis is cyclophosphamide. This alkylating agent, when administered intravenously, can cause hyponatremia, impairing water excretion by potentiating the effect of ADH and possibly by increasing its release. Patients on cyclophosphamide therapy are at high risk of developing hyponatremia because they are encouraged to drink large amounts of fluids to maintain high urine output as an effort to prevent chemical cystitis. The combination of both increased ADH effect and water intake can induce potentially life-threatening water intoxication. Administration of isotonic saline solution instead of using water is an

appropriate measure to minimize the incidence of this complication.⁴⁵⁻⁴⁷

It should be emphasized that in patients with chemotherapy-related hyponatremia, chemotherapy-induced nausea may have an important role because nausea is a potent stimulus to ADH release. Moreover, immunomodulators, including interferon, interleukin 2, and levamisole, as well as monoclonal antibodies, also were shown to induce hyponatremia.⁴² The underlying mechanism in the majority of cases seems to be SIADH. Finally, methotrexate in high doses can cause hyponatremia. A toxic effect on the neurosecretory areas of the cerebrum, as well as alteration of the distribution of body fluid volumes, was proposed as a possible explanation of methotrexate-induced hyponatremia.⁵⁰

Analgesics. Morphine and other opiates have often been implicated as a cause of hyponatremia, possibly by directly enhancing ADH release.⁵¹ In addition, indirect stimulation of ADH secretion caused by opiate-induced nausea or hypotension may occur.

Drugs that Potentiate the Effect of Endogenous ADH at the Renal Tubule Level

Antiepileptic drugs. It was proposed that carbamazepine may cause hyponatremia by increasing renal sensitivity to normal plasma ADH concentrations.³⁰⁻³³ Lamotrigine also may potentiate renal tubule effects of ADH.⁵²

Hypoglycemic agents. Chlorpropamide, which is now rarely used in the treatment of patients with diabetes mellitus, can cause hyponatremia in approximately 4% to 6% of patients with clinical characteristics of SIADH. Elderly patients concomitantly using diuretics have greater risk of developing hyponatremia.⁵³⁻⁵⁵ Tolbutamide can cause hyponatremia by decreasing renal free water clearance.⁵⁶ It is worth mentioning that although fluid retention is a common adverse effect of both thiazolidinediones (pioglitazone and rosiglitazone), hyponatremia related to these drugs was not reported yet. Finally, there is only 1 case report with metformin-related hyponatremia.⁸⁸

Anticancer agents. In addition to increasing ADH release, intravenous cyclophosphamide can cause hyponatremia by potentiating the effect of ADH.⁴⁶

Nonsteroidal anti-inflammatory drugs. Nonsteroidal anti-inflammatory drugs (NSAIDs) decrease water excretion by potentiating the effect of ADH. This is caused by a decrement in renal prostaglandin synthesis because prostaglandin normally is an inhibitor of ADH action. It should be noted that hyponatremia attributable exclusively to NSAIDs is rare, probably because prostaglandin inhibition also may directly suppress ADH secretion centrally. However, volume-depleted patients or those with SIADH simultaneously using this group of medications have increased risk of developing hyponatremia.^{57,58} Additionally, it appears that NSAIDs are a risk factor for hyponatremia in ultramarathon and marathon runners.⁵⁹ This association was described during military operations and desert hikes. Such individuals also may be using NSAIDs, which can impair the excretion of free water. Ultramarathon and marathon runners may replace their dilute, but sodium-containing, sweat losses with excessive amounts of hypotonic solutions, with the net effect of a decrease in plasma sodium concentration. However, the risk of hyponatremia in runners using NSAIDs was not shown in all studies.⁶⁰

Drugs that Reset the Osmostat

Hyponatremia caused by a reset osmostat syndrome variant of SIADH has been described after treatment with carbamazepine,³³ and venlafaxine, a serotonin and norepinephrine reuptake inhibitor.⁶¹

Drugs Inducing Labor

Oxytocin, used to induce labor or abortion, has significant antidiuretic activity. Therefore, when administered with excess electrolyte-free water, hyponatremia is a possible consequence.⁸⁹⁻⁹¹ This complication can be prevented by decreasing the amount of water given and using isotonic saline, rather than dextrose and water. Moreover, administration of exogenous ADH (as part of the treatment of patients with gastrointestinal hemorrhage) also can cause hyponatremia. Finally, hyponatremia can be induced by desamino-8-D-AVP (an analogue of ADH), which is used for either polyuria in patients with central diabetes insipidus or bleeding caused by platelet dysfunction (von Willebrand disease).^{92,93}

Drug-induced Dilutional or Translocational Hyponatremia

In some cases, the decrease in serum sodium levels is associated with normal or increased effective plasma osmolality, rather than hypo-osmolality. This was called dilutional or translocational hyponatremia. Administration of hypertonic mannitol is an example of pseudohyponatremia with increased plasma osmolality. Mannitol (by increasing plasma osmolality) creates a transcellular osmotic gradient, resulting in water movement out of the cells and decrease in serum sodium concentration by means of dilution.

Rare Causes of Drug-induced Hyponatremia

Apart from agents listed in Table 1, there are sporadic case reports of numerous other drugs that can cause hyponatremia. Some of these relatively rare causes of drug-induced hyponatremia are listed in Table 2.

Angiotensin-Converting Enzyme Inhibitors

It is worth mentioning that angiotensin-converting enzyme (ACE) inhibitors in combination with furosemide were shown to correct hyponatremia in patients with congestive heart failure. However, ACE inhibitors per se can cause hyponatremia. A handful of cases of ACE inhibitor-related hyponatremia was reported.⁶² These drugs inhibit the conversion of angiotensin I to angiotensin II in peripheral tissue, but not the brain. In the brain, angiotensin I is converted to angiotensin II, which may stimulate thirst and the release of ADH. Additionally, ACE inhibitors induce an increase in ADH secretion by delaying the degradation of bradykinin.

Immune Globulin

It is well known that hyperlipidemia or hyperproteinemia can induce pseudohyponatremia. Furthermore, intravenous infusion of immune globulin increases the protein-containing nonaqueous phase of plasma, with a consequent relative decrease in plasma water volume. Because sodium is present in only the aqueous phase, each unit volume of plasma measured has less sodium-containing water, and this is interpreted as hyponatremia. Newer methods using ion-selective electrodes for the measurement of serum electrolytes may avoid this problem and give accurate

results if measured in undiluted samples (direct potentiometry).

Intravenous immune globulin frequently is administered in a 10% maltose solution. Maltose normally is metabolized by maltase in proximal tubules. However, in patients with renal failure, maltose accumulates in extracellular fluid, increasing plasma osmolality and diminishing serum sodium levels by means of dilution.⁶⁴ Translocational (hyperosmotic) hyponatremia also can be observed with sugar-containing intravenous immune globulin administration. It appears that the magnitude of hyponatremia depends considerably on the degree of renal impairment during intravenous immune globulin infusion. In the setting of impaired renal function, decreased renal clearance of sucrose takes place, leading to increased effective plasma osmolality.⁶⁵ Finally, intravenous administration of immune globulin also can cause hyponatremia because of aseptic meningitis-related SIADH.⁶⁵

Amphetamines

Abuse of 3,4-methylenedioxymethylamphetamine (MDMA), also known as ecstasy, is an increasingly recognized cause of severe hyponatremia. MDMA and its metabolites were shown to induce enhanced ADH secretion from the hypothalamus. The excessive water intake (to counteract hyperthermia) is common in MDMA users and is involved in the pathogenesis of MDMA-induced hyponatremia.^{66,67}

Co-Trimoxazole

Trimethoprim-sulfamethoxazole (co-trimoxazole) is known to cause hyperkalemia and, less frequently, hyponatremia. These electrolyte disturbances take place more often in patients administered high doses of trimethoprim-sulfamethoxazole and those with renal dysfunction. Trimethoprim acts as a potassium-sparing diuretic by blocking the amiloride-sensitive sodium channels in the distal tubule. Consequently, the mild hyponatremia observed in patients administered trimethoprim should be attributed to ongoing sodium losses that lead to hypovolemia and increased ADH secretion.⁶⁸

Amiodarone

Hyponatremia is a rare adverse effect of amiodarone therapy. SIADH is the possible underlying mechanism. It was proposed that amiodarone might cause SIADH through its channel-modulating properties on neural or renal tissues. Amiodarone-induced hyponatremia occurs mainly during the first weeks of therapy or even during the loading period. It is worth mentioning that SIADH also was reported in association with other antiarrhythmic drugs, such as lorcaïnide and propafenone.⁷²⁻⁷⁴

Calcium Channel Antagonists

In theory, calcium channel antagonists with natriuretic properties could cause hyponatremia. A case of amlodipine-associated hyponatremia has been reported.⁶³ However, that patient also received amiodarone, which had not been recognized as a cause of hyponatremia at the time of publication. Consequently, calcium channel antagonist-related hyponatremia, if it exists, is extremely rare.

Theophylline

Theophylline-induced hyponatremia has rarely been described. Theophylline inhibits solute reabsorption in both the proximal nephron and diluting segment, with a thiazide-like action. Furthermore, theophylline can cause hypokalemia, especially in patients with acute intoxication. Depletion of potassium is expected to contribute to hyponatremia because sodium concentration is determined by the ratio of “exchangeable” (ie, osmotically active) portions of the body’s sodium and potassium content to total-body water. It also was proposed that potassium depletion shifts sodium to the intracellular space. Additionally, theophylline-associated SIADH is probable.⁷⁵

Proton Pump Inhibitors

Proton pump inhibitors (PPIs) also can cause hyponatremia. Currently, only 9 cases of PPI-induced hyponatremia have been reported in the literature.⁷⁶ Consequently, hyponatremia is an extremely rare adverse effect of PPIs, taking into consideration that this class of drugs is widely prescribed. In all except 1 case, omeprazole was the cause of hyponatremia, whereas 1 case was ascribed to esomeprazole. The underlying patho-

physiological mechanism of hyponatremia is not entirely clear, but is believed to be SIADH. Salt-losing nephropathy has also been proposed as a possible mechanism of PPI-related hyponatremia given that these drugs are now the most common cause of drug-induced acute interstitial nephritis. However, causality between PPI-induced hyponatremia and renal salt wasting was not definitively proved yet.⁷⁶

CONCLUDING REMARKS

Hyponatremia occasionally may develop in the course of treatment with drugs used in everyday clinical practice (eg, newer antihypertensive agents, antibiotics, and PPIs). It should be noted that patients may receive complex drug regimens (eg, patients with diabetes mellitus) containing several candidates as the cause of hyponatremia. Discontinuation of treatment with these agents and avoidance of readministration is fully warranted. It is recommended that patients with acute severely symptomatic hyponatremia (eg, seizures) should be treated in an aggressive but controlled fashion, whereas less symptomatic hyponatremia may be corrected at a slower pace.⁹⁴ Most authorities advocate as a therapeutic target in all cases to limit the increase in serum sodium concentration to less than 12 mEq/L (<12 mmol/L) in the first day and less than 18 mEq/L (<18 mmol/L) in the first 2 days of treatment, as well as avoid overcorrection of serum sodium concentration to greater than 140 mEq/L (>140 mmol/L) within the first 2 days of treatment.⁹⁴ Nonetheless, awareness of the adverse effect of certain pharmaceutical compounds on serum sodium concentrations facilitates a rational clinical management.

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