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In-Depth Clinical Review

A review of drug-induced hypernatraemia

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Abstract

Drug-induced electrolyte abnormalities have been increasingly reported and may be associated with considerable morbidity and/or mortality. In clinical practice, hypernatraemia (serum sodium higher than 145 mmol/L) is usually of multifactorial aetiology and drug therapy not infrequently is disregarded as a contributing factor for increased serum sodium concentration. Strategies to prevent this adverse drug effect involve careful consideration of risk factors and clinical and laboratory evaluation in the course of treatment. Herein, we review evidence-based information via PubMed and EMBASE and the relevant literature implicating pharmacologic treatment as an established cause of hypernatraemia and discuss its incidence and the underlying pathophysiologic mechanisms.

Keywords: adverse drug reaction; diabetes insipidus; hypernatraemia; sodium homeostasis

Introduction

Hypernatraemia, defined as a serum sodium level >145 mmol/L, is a relatively common electrolyte disorder, especially among the elderly and critically ill patients. The reported frequency of hypernatraemia in a general hospital population ranges from 0.3% to 3.5% [1,2]. Patients admitted to the intensive care unit (ICU) have a higher incidence of hypernatraemia that has been reported to be as high as 8.9% [3]. It is also characterized by increased mortality. In fact, the reported mortality rates range from 40% to higher than 60% [1]. Drugs, not infrequently, represent a cause of electrolyte abnormalities, and a careful drug history is essential in patients with acid–base and electrolyte derangements. Hypernatraemia is often of multifactorial origin, while drugs constitute one of the most common offending or contributing factors for increased serum sodium concentration.

Herein, we review evidence-based clinical information on the incidence of hypernatraemia associated with specific drug treatment and discuss the underlying pathophysiologic mechanisms and potential therapeutic implications.

Data extraction and synthesis

Finding relevant studies

Two reviewers (G.L. and H.J.M.) independently searched for relevant articles in PubMed and EMBASE (up to February 2009) bibliographic databases. The search strategy was based on the combination of 'hypernatremia', 'drug', 'drug-induced', 'adverse drug reaction' and 'adverse drug effect'. Any article considered relevant by any reviewer was evaluated, references of retrieved articles were screened and relevant and representative information was included.

Study selection

Studies were included if the two reviewers independently agreed that an article met established requirements including (a) any type of article (including, clinical studies, reviews and case reports with at least one subject), (b) English language, (c) exposure to drugs or fluids, (d) documented hypernatraemia (serum sodium >145 mmol/L) either symptomatic or asymptomatic. Disagreements were resolved by a third reviewer (M.E.) or by consensus.

Results

A total of 413 abstracts were screened, and 222 potentially relevant full-text articles were retrieved. Ninety articles referring to hypernatraemia associated with drug therapy were selected. They included 29 case reports, and 23 clinical studies. The most frequently reported causative agents were lithium (12 articles), followed by amphotericin (8 articles), vasopressin V_2-receptor antagonists (4 articles), mannitol (4 articles), lactulose (4 articles) alcohol (3 articles).

Pathogenetic aspects of hypernatraemia

Hypernatraemia is a hyperosmolar state. The physiologic response to hypertonicity (through the activation of hypothalamic osmoreceptors) is the stimulation of both

antidiuretic hormone (ADH) release and thirst [4]. Sequentially, water excretion diminishes and water ingestion increases resulting in water retention and return of the serum sodium concentration to normal [4].

Osmoregulation is normally as efficient as to keep the plasma osmolality (Posm) in the very narrow range of 280–290 mosmol/kg despite a great variation in sodium and water intake. The renal-concentrating mechanism is the first defence against water depletion and hyperosmolality. However, the ultimate protection against progressive and sustained hypernatraemia is the stimulation of thirst [5]. Indeed, patients with diabetes insipidus, in whom the urine output can exceed 10–15 L/day, maintain a near-normal serum sodium level by appropriately increasing water intake to replace very large urinary water losses [5]. Consequently, it is obvious that the excess renal water loss does not cause hypernatraemia on the condition that the water intake is not impaired or prevented. As a result, hypernatraemia is observed in patients with hypodipsia or, much more frequently, in adults with altered mental status and in infants [1,6]. Elderly people represent a group at increased risk of hypernatraemia due to a diminished osmotic stimulation of thirst. Moreover, concurrent diseases and impaired mental status, which not infrequently are encountered in the elderly, increase the possibility of hypernatraemia [1,6].

Total exchangeable sodium (Na_e^+), total exchangeable potassium (K_e^+) and total body water (TBW) are the major determinants of plasma water sodium concentration according to the Edelman equation: plasma water $[Na^\pm] = 1.11(Na_e^\pm \pm K_e^\pm)/TBW - 25.6$ [7]. Although most cases are due to water loss, hypernatraemia can be occasionally due to the administration of hypertonic sodium solutions [8]. However, it is well known that net water loss (if not replaced), either in the absence of a sodium deficit (pure water loss) or in its presence (hypotonic fluid loss), accounts for the majority of cases of hypernatraemia [8].

An increase in serum sodium concentration creates an osmotic gradient between the extracellular and intracellular fluid in brain cells causing movement of water into the extracellular space in order to maintain the osmotic equilibrium at the expense of a decrease in the cell volume [9,10]. Thus, the symptoms of hypernatraemia (predominantly neurological) are attributed to brain cell shrinkage and are related to both the severity and the rapidity of the rise in the serum sodium level [9,10].

Drug-induced hypernatraemia

Several medications have been identified as causes of hypernatraemia. Nonetheless, in hospitalized patients, the aetiology of hypernatraemia is usually multifactorial and drug therapy may be disregarded as a contributing factor for increased serum sodium concentration.

Drugs may cause hypernatraemia due to free water loss; rarely hypernatraemia may result from the administration of hypertonic sodium solutions (Table 1).

Table 1. Principal causes and the underlying mechanisms of drug-induced hypernatraemia

A. Water loss
1. Renal losses
(i) Acquired nephrogenic diabetes insipidus
   Drug-induced hypokalaemia: diuretics, cisplatin, aminoglycosides, amphotericin B, penicillin derivatives
   Drug-induced hypercalcaemia: lithium, vitamin A or D excess
   Other drugs: lithium, demeclocycline, amphotericin B, foscarnet, colchicine, vinblastine, vasopressin V_2-receptor antagonists
(ii) Central diabetes insipidus
   Lithium, phenytoin, ethanol
(iii) Other causes
   Loop diuretics
   Osmotic diuresis
   Mannitol administration
   Nutritional supplementation
   Urea
   Agents that cause increased production of urea: corticosteroids, high-protein supplements
2. Gastrointestinal losses
   Osmotic cathartic agents: lactulose, sorbitol
B. Hypertonic sodium gain
   Hypertonic sodium bicarbonate infusion
   Hypertonic sodium chloride infusion
   Hypertonic feeding preparation
   Sodium chloride-rich emetics
   Hypertonic saline enemas
   Intrauterine injection of hypertonic saline
   Hypertonic saline irrigation of intra-abdominal hydatid cysts
   Hypertonic dialysis
   N-acetylcysteine

Available evidence originates in small studies and case reports.

Drugs inducing renal water loss

Drug-induced acquired nephrogenic diabetes insipidus

It is known that ADH is secreted by the posterior pituitary. ADH acts on the collecting duct of the kidney to increase water reabsorption [11]. Transcellular water reabsorption is mediated by water channels (aquaporins, AQP). Diabetes insipidus is owing to a defect in the secretion (and usually in the synthesis) of ADH in response to increased osmolality (hypothalamic or central diabetes insipidus, CDI) [12] or a lack of an otherwise normal kidney to respond to normal plasma ADH levels (nephrogenic diabetes insipidus, NDI) [13]. As a consequence, the kidney loses its concentrating ability and produces large volumes of hypotonic urine (3–20 L/day). Polyuria, with hyposthenuria, and polydipsia are the cardinal clinical manifestations of the disease, while the vast majority of patients are normonatraemic provided that their thirst mechanisms are intact [12,13]. However, these subjects are at risk of hypernatraemia if their fluid intake is restricted and if they receive inadequate intravenous fluid peri-operatively or during episodes of vomiting or diarrhoea or during acute illness.

A variety of medications have been reported to induce acquired nephrogenic diabetes insipidus (Table 1). Studies have shown that in acquired forms of NDI, the underlying urinary concentrating defect results from decreased

expression of AQP-2 or impaired delivery of these channels to the apical plasma membrane [11].

Drugs inducing hypercalcaemia or hypokalaemia (Table 1). Hypercalcaemia (when serum calcium concentration exceeds 11 mg/dL, 2.75 mmol/L) and *hypokalaemia* (when a serum potassium levels is <3 mmol/L) can cause NDI that is, in the majority of cases, reversible within 1–12 weeks after the restoration of these electrolyte disorders [14]. It has been reported that hypokalaemia and hypercalcaemia reduce the expression of AQP-2 in the distal collecting tubules of the nephron responsible for the antidiuretic mechanism [15,16]. The polyuria observed with these electrolyte disturbances should be ascribed not only to the concentrating defect but also to a direct stimulation of thirst as a result of hypokalaemia and possibly hypercalcaemia [17].

Lithium. Lithium (Li) is the commonest drug causing hypernatraemia; serum sodium levels as high as 196 mmol/L have been reported [18]. Li is used to treat bipolar (manic-depressive) disorders and has become the most frequent cause of drug-induced NDI. NDI is evident in almost 50% of patients receiving prolonged lithium therapy [18]. Of those, 30% have a subclinical concentrating defect, while the remaining 20% suffer from polyuria that can take place within the first 8–12 weeks of treatment. Lithium-induced NDI is usually reversible upon stopping therapy, but a few patients remain symptomatic long after discontinuation of Li [19]. In a series of 23 cases of Li intoxication, three patients developed hypernatraemia ranging from 155 mmol/L to 162 mmol/L [20]. Water loss due to impaired renal concentrating ability was implicated in the pathogenesis of hypernatraemia.

Li induces NDI by inhibiting adenyl cyclase in the principal cells of the distal tubule and collecting duct of the kidney thereby decreasing cyclic adenosine monophospate (cAMP) and protein kinase A stimulation [21]. The net result is a downregulation of AQP-2 thereby reducing the abundance of water channels in the apical membrane of the cells and subsequent water transport. However, in a cell model to study lithium-induced NDI, it has recently been shown that the lithium-induced downregulation of AQP-2 and the development of NDI may occur independent of the adenylyl cyclase activity *in vitro* and *in vivo* [22].

Hypercalcaemia associated with Li treatment may potentially increase the risk of NDI. In addition, Li may affect water homeostasis by producing a primary polydipsia [23] and possibly by inhibiting CNS release of ADH [24].

Demeclocycline. Demeclocycline, a tetracycline derivative, at a dose of 900–1200 mg/day for several days can cause NDI in almost all cases. Polyuria usually has a gradual onset and may not be apparent for several days [25]. The concentrating defect is dose dependent and fully reversible within a few weeks after the drug withdrawal [25]. This side effect has made demeclocycline useful in the treatment of hyponatraemic patients due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) [26].

Amphotericin B. Among other toxic effects on the kidney [27] (albuminuria, renal tubular acidosis, hypomagnesaemia, hypokalaemia and elevation in serum creatinine), the antifungal agent amphotericin B can also induce NDI. Amphotericin B is believed to have a direct effect on adenylyl cyclase and AQP-2 [28]. Amphotericin-induced defect in urinary concentration may in part be causally related to a reduced abundance of AQP-2 channels in the kidney [28]. These effects are totally reversible after the discontinuation of treatment [29] or replacement with liposomal amphotericin B [30,31]. On the other hand, high-dose liposomal amphotericin B has also been implicated in the development of NDI [32]. In a series of 116 neutropaenic patients treated with liposomal amphotericin B, hypernatraemia due to amphotericin was confirmed in 17 patients (14.6%) [33].

Other agents. In theory, any drug that causes NDI may provoke hypernatraemia. Although ifosfamide, ofloxacin and orlistat are regarded as established causes of NDI, there are currently no reports of drug-induced hypernatraemia associated with their use [34]. NDI and hypernatraemia have been reported with high doses of the antiviral agent foscarnet [35]. Ingestion of a high dose of colchicine due to a suicide attempt has been described to cause hypernatraemia (up to 160 mmol/L) and polyuria in a previously healthy individual [36]. There are experimental data showing that colchicine and vinbalstine, which disrupt intracellular microtubules, inhibit vasopressin- and cAMP-mediated water flow in the mammalian kidney. The integrity of cytoplasmic microtubules in cells of the distal nephron is required for the antidiuretic action of vasopressin, probably at steps distal to cAMP generation [36].

Finally, in light of the approval of *vasopressin V_2-receptor antagonists* as therapy of euvolaemic or hypervolaemic hyponatraemia, these therapeutic agents should also be considered as a possible cause of hypernatraemia. In two clinical trials [37,38], hypernatraemia occurred in as many as 1.8% of patients receiving treatment with tolvaptan. However, in another study in patients with acute and chronic heart failure treated with tolvaptan, hypernatraemia developed in 6% of patients treated with 30 mg/day, 11% of those receiving 45 mg/day and 13% in the 60 mg/day group compared with 5% in the placebo-treated group [39]. It appears that the risk of excessive sodium correction or hypernatraemia exists with all the V_2-receptor antagonists, especially if combined with fluid restriction [40].

Drug-related central diabetes insipidus (Table 1)

It is known that phenytoin (diphenylhydantoin) and ethanol have a transient inhibitory effect on ADH release. Ethanol has also been suggested to cause NDI rather than CDI [34].

Severe hypernatraemic coma has been described in a patient receiving toxic doses of phenytoin [41]. Patients taking phenytoin are not polyuric. On the other hand, phenytoin has been shown to reverse hyponatraemia induced by carbamazepine therapy [42]. Of note, the acute administration of phenytoin has no significant influence on carbamazepine-induced antidiuresis. Reversal of the antidiuretic effect of carbamazepine by chronic phenytoin administration is

secondary to a marked reduction in the serum carbamazepine concentration during combined therapy [43].

Hypernatraemia has infrequently been described in patients with chronic alcohol abuse. In a series of 241 consecutive alcoholic patients studied prospectively, hypernatraemia was documented in 2.5% of patients [44]. However, the prevalence of hypernatraemia has been reported to be remarkably higher in patients presenting with acute alcohol intoxication; hypernatraemia was diagnosed in 15.3% in a retrospective study of 196 alcohol intoxications treated in hospital [45] and culminated to 41% in an Austrian study of patients admitted to the emergency room over a 6-month period [46].

Other causes

Examples of hypotonic renal losses include osmotic diuresis and the administration of loop diuretics. Hyperglycaemia (with glucosuria) and infusion of hypertonic mannitol represent common causes of osmotic diuresis. The presence of large amounts of non-reabsorbed solute in the tubular lumen leads to enhanced urinary water loss. The increase in urine output induced by the excess solutes results in a dilutional fall in the urine sodium and potassium concentration to a level below that in the plasma. Consequently, plasma sodium concentration rises due to loss of water in excess of sodium and potassium unless there is a concomitant increase in fluid intake [47]. A similar problem is encountered in patients on enteral tube feedings with high protein content. Reported incidence of hypernatraemia in this clinical setting ranges from 0.65% to 10% [48,49]. Hypernatraemia may result either from diarrhoea, hyperglycaemia with glycosuria, or from osmotic diuresis from high protein supplementation. Both hyperglycaemia and inadequate free water intake have been reported in patients receiving total parenteral nutrition [48,49]. Similarly, most cases of diarrhoea-associated hypernatraemia resulted from inadequate replacement of free water.

Patients with stroke and altered mental status are at high risk of severe hypernatraemia. These patients usually receive normal saline plus/minus potassium chloride, while hypotonic solutions are avoided in stroke patients in order to prevent or further deteriorate cerebral oedema [2]. Moreover, mannitol is also given to correct cerebral oedema, if present. In subjects unable to drink water, hypernatraemia results from insensible losses in combination with the ongoing mannitol-induced renal hypotonic losses coupled with the administration of isotonic or hypertonic solution. In fact, the addition of potassium chloride significantly increases the osmolality of administered fluids [1 L of 0.9% sodium chloride plus potassium chloride (two ampules containing 13.5 mmol/L of potassium each) results in an osmolality of 360 mmol/L H_2O] [9,50]. In such cases, hypernatraemia occurs if urine osmolality (Uosm) is lower than that of plasma (Posm). The administration of mannitol constitutes a significant contributing factor for or cause of in-hospital hypernatraemia ranging from 7% [1] to 21% [51] of hospitalized hypernatraemic patients.

Loop diuretics represent another cause of hypotonic renal losses. In general, hypernatraemia is a relatively rare adverse effect of loop diuretic administration given that these agents are short acting, while free water losses can be easily replaced by means of increased water intake. In a series of 162 hypernatraemic patients, 13 developed hypernatraemia in the course of loop diuretic treatment [52]. These agents inhibit NaCl reabsorption in the thick ascending limb of the loop of Henle thereby reducing the osmolarity of the medullary interstitium that results in an impairment of the renal concentrating mechanisms. Treatment of the syndrome of inappropriate antidiuresis (SIADH) with furosemide or urea can also be complicated with hypernatraemia [53,54].

A recent 1:2 matched case–control study included 130 cases of hypernatraemia developed in the intensive care unit (ICU) compared to 260 controls. The most common causes independently associated with hypernatraemia were sepsis (9% in cases versus 2% in controls), hypokalaemia (53% versus 34%), renal dysfunction (53% versus 13%), hypoalbuminaemia (91% versus 55%), mannitol (10% versus 1%) and the use of sodium bicarbonate (23% versus 0.4%) ($P < 0.05$ for all) [55]. Of note, during the development of hypernatraemia, fluid balance was negative in two-thirds of the cases, but positive in one-third, which is higher than usually proclaimed [55].

Gastrointestinal causes

Hypernatraemia may complicate the use of the osmotic cathartics lactulose and sorbitol that are commonly used in the treatment of hepatic encephalopathy or drug intoxications, respectively. In these settings, water is lost in excess of sodium plus potassium resulting in reduction of TBW without commensurate reduction in Na_e^+ and K_e^+, thus leading to increased plasma sodium according to the Edelman equation [56,57]. Taking into consideration that the mental status is often impaired in the course of hepatic encephalopathy or drug overdose, these stool water losses not infrequently remain unreplaced resulting in an increase in the serum sodium concentration [56,57]. In a series of 113 hypernatraemic patients, the contribution of lactulose regarding the development of hypernatraemia was 7.7% [51].

Agents that cause hypertonic sodium gain

Pure hypertonic saline gain is a relatively unusual cause of hypernatraemia [58]. It is the consequence of accidental or intentional ingestion of hypertonic solutions. We have described a 24-year-old woman who survived after an erroneous infusion of hypertonic sodium solution (sodium chloride 15%) prior to the delivery of her baby. The net result was a dramatic rise in serum sodium from 136 to 178 mmol/L [59]. The discontinuation of this solution and the administration of dextrose 5% followed by furosemide, 20-mg bolus, intravenously were effective in normalizing serum sodium without neurological sequelae and complications during delivery [59].

Acute hypernatraemic states have been described as a complication of hypertonic saline induction of abortion either by intra-amniotic injection or intravascular saline

infusion [60]. Serum sodium levels during these events have been reported to be as high as 185 mmol/L [61].

Other examples of iatrogenic hypernatraemia include the infusion of hypertonic sodium bicarbonate to treat metabolic acidosis or during resuscitation [62,63], and hypertonic saline irrigation of intrahepatic hydatid cysts. In the latter cases, hypernatraemia probably results from absorption of hypertonic saline through the cyst walls and from exchange of both salt and water through the peritoneal membrane. Serum sodium levels up to 200 mmol/L and fatal outcome due to central myelinolysis have been described [64,65].

A series of 12 children incurring non-accidental salt poisoning have been reported by Meadow [66]. These children presented in the first 6 months of life with unexplained hypernatraemia and associated illness. Most of them suffered repetitive poisoning and the perpetrator was believed to be the mother in 10 cases. Four of them had serum sodium concentrations above 200 mmol/L and two of them died. According to Meadow [66], salt poisoning is essentially a problem of infants and younger children, firstly because the immature kidney has a limited ability to excrete a sodium load and secondly because an infant or young child can be denied access to water. Thus, for young children, salt poisoning tends to be a combination of excess salt ingestion and restriction of fluid intake.

Hypertonic phosphate enemas have been shown to cause marked hypernatraemia in infants and elderly individuals [67–69]. Hypernatraemia due to increased sodium absorption has been reported in a case of a premature infant treated for meconium ileus with *N*-acetylcysteine enema [70]. Not surprisingly, by administering 33.5 mmol of sodium per kg daily to the patient, the serum sodium concentration rose from 135 to 163 mmol/L [70].

Massive salt ingestion as can occur with the ingestion of a highly concentrated saline emetic or gargle has been associated with severe and even lethal hypernatraemia [71]. Severe hypernatraemia (up to 245 mmol/L) has been detected in this setting [72]. Voluntary salt intake in adults has been linked to female gender and psychiatric disorders. Serum sodium levels ranging from 153 to 255 mmol/L have been documented [73]. In a review of the relevant literature of 17 adult patients with severe hypernatraemia secondary to excessive salt ingestion, it was found that only 2 survived. Case fatality was strongly associated with serum sodium levels [73].

Therapeutic measures

Strategies to prevent drug-induced hypernatraemia should involve careful consideration of risk factors and clinical and laboratory evaluation in the course of treatment. We should always keep in mind that hypernatraemia is a condition of considerable morbidity and mortality. Reports of the mortality rate vary depending on the acuteness and magnitude of hypernatraemia. Thus, among adult patients with serum sodium levels increased to at least 160 mmol/L in <24 h, the reported mortality rate was >70%, while the mortality rate was 60% in those with sodium exceeding 160 mmol/L in 48 h and 46% in subjects with serum

sodium levels >150 mmol/L developing over 48 h [1,74–76]. However, hypernatraemia is not always detrimental. For example, moderate hypernatraemia is sometimes induced by mannitol in neurosurgical patients to control intracranial pressure [2]. In addition, hypernatraemia may be beneficial in the course of diabetic ketoacidosis when it maintains the effective osmolality (that is, a rise in serum sodium can compensate for a fall in serum glucose, thereby maintaining effective osmolality) and may even prevent cerebral oedema [77].

When hypernatraemia occurs acutely, the volume of all body cells is reduced in proportion to the degree of hypernatraemia. Hyperacute hypernatraemia (occurring within <12 h) may be treated rapidly. However, it is unlikely that any associated damage (e.g. brain haemorrhage) will be reversed by rapid treatment [78]. When hypernatraemia is chronic (i.e. present for >2 days), body cells, including brain cells and red blood cells, restore their volumes to normal through volume regulatory mechanisms. Thus, in chronic hypernatraemia, these cells have normal volumes with increased intracellular solute content. When the osmolality is abruptly normalized, the cell volume increases to a supernormal size that may lead to brain oedema and herniation. It is therefore recommended that chronic hypernatraemia should be treated slowly [78].

The current therapeutic options of acquired drug-related NCI are limited and are only partially beneficial. The discontinuation of treatment with implicated drugs and the restoration of possible underlying electrolyte disturbances (hypokalaemia, hypercalcaemia) is fully warranted. Moreover, ensuring adequate water ingestion is of paramount importance. However, this is difficult to achieve at the extremes of age if the patient cannot sense thirst and obtain water. Exogenous vasopressin (ADH) is not effective due to the failure of the kidney to respond to ADH. It should be noticed that a combination of a very low sodium diet along with a thiazide diuretic (by diminishing the water delivery to the collecting tubules as a result of volume depletion-associated enhanced proximal NaCl and water reabsorption) as well as the usage of nonsteroidal anti-inflammatory drugs (possibly by normalizing the prostaglandin levels, which frequently are elevated in patients with NDI) may partially decrease urine volume [79,80]. In patients with lithium-induced NDI, the addition of amiloride is also beneficial. Amiloride reduces lithium uptake into principal cells in the collecting duct, which diminishes the inhibitory effect of intracellular lithium on the production of cAMP and water reabsorption [81]. Finally, amiloride, a potassium-sparing diuretic, lessens the need for potassium supplementation that is usually required when thiazides are used to treat polyuria [82].

It is recommended that in patients with symptomatic hypernatraemia developed over a period of <48 h, a rapid correction of serum sodium concentration (1–2 mmol/L/h) should initially be performed, while a slower rate of serum sodium reduction (<0.5 mmol/L/h) should be attained in patients with hypernatraemia of longer or unknown duration [51,82–85]. In general, most authorities advocate as a therapeutic target to limit the decrease in the serum sodium concentration to <12 mmol/L per day. Patients with severe

hypovolaemia (e.g. patients with hypotension and oliguria) should initially be treated with isotonic (0.9%) saline (until the stabilization of the haemodynamic status) followed by 0.45% saline administration, while milder volume deficit should be corrected with half- or quarter-isotonic saline. Moreover, 5% dextrose in water intravenously (or by drinking water in subjects able to take fluids orally) either alone or in combination with furosemide is employed in euvolaemic and hypervolaemic hypernatraemia, respectively [51,82–85].

The amount of water necessary to correct hypernatraemia is estimated using the following equation: water requirement (L) = TBW × [(Na$_s^+$/140) − 1], where Na$_s^+$ represents the patient's serum sodium concentration (mmol/L). The TBW (L) is estimated as 60 and 50% of lean body weight in men and women, respectively, while in water-depleted hypernatraemic patients (namely subjects without hypervolaemic hypernatraemia), lower values (50% of lean body weight in men and 40% in women) should be used. For example, in a man presenting with hypervolaemic hypernatraemia (serum sodium 162 mmol/L), and a body weight of 80 kg, the amount of water necessary to correct hypernatraemia is $0.6 \times 80 \times [(162/140) − 1] = 7.5$ L. Thus, administration of 7.5 L of free water to decrease the serum sodium concentration by 22 mmol/L should take place over a minimum of 44 h, which represents a rate of fluid administration of 170 mL/h. The estimated insensible losses (usually 30–50 mL/h) should also be replaced raising the infusion rate of free water to 200–220 mL/h. Moreover, furosemide 0.5–1 mg/kg should be administered intravenously. If the above-mentioned patient has euvolaemic hypernatraemia, the water deficit is $0.5 \times 80 \times [(162/140) − 1] = 6.3$ L. Therefore, 175–195 mL/h of 5% dextrose is required. Finally, if the aforementioned subject presented with mild hypovolaemic hypernatraemia, half-isotonic (350–390 mL/h) or quarter-isotonic saline (235–260 mL/h) should be administrated in order to provide 175–195 mL/h of free water, taking into consideration that 1 L of half-isotonic or quarter-isotonic saline contains 500 mL or 750 mL of water, respectively. Any ongoing gastrointestinal losses should also be replaced. Determining the volume status of the patient (e.g. hypotension and tachycardia in cases of hypovolaemic hypernatraemia or pressure-induced oedema in hypervolaemic states) and measuring the urine osmolality and urine sodium may offer clinical clues as to the diagnosis and to the therapeutic approach. However, when the calculated difference in water deficit is relatively small (<1 L), the correction 0.6 versus 0.5 may not be feasible.

Conclusion

Hypernatraemia may occasionally develop in the course of treatment with drugs used in everyday clinical practice (including lithium, lactulose, mannitol). However, it is entirely clear that a careful oversight of the use of these agents is required especially in high-risk patients for the development of hypernatraemia (e.g. elderly, mentally handicapped, critically ill). Nonetheless, awareness of the adverse effect of certain pharmaceutical compounds on serum sodium concentrations facilitates a rational clinical management.

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