Pathophysiology of Drug-Induced Hyponatremia

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Drug-induced hyponatremia caused by renal water retention is mainly due to syndrome of inappropriate antidiuresis (SIAD). SIAD can be grouped into syndrome of inappropriate antidiuretic hormone secretion (SIADH) and nephrogenic syndrome of inappropriate antidiuresis (NSIAD). The former is characterized by uncontrolled hypersecretion of arginine vasopressin (AVP), and the latter is produced by intrarenal activation for water reabsorption and characterized by suppressed plasma AVP levels. Desmopressin is useful for the treatment of diabetes insipidus because of its selective binding to vasopressin V2 receptor (V2R), but it can induce hyponatremia when prescribed for nocturnal polyuria in older patients. Oxytocin also acts as a V2R agonist and can produce hyponatremia when used to induce labor or abortion.

aquaporin-2 kidney nephrogenic antidiuresis vasopressin V2 receptor water

1. Introduction

Hyponatremia, which is defined as a serum sodium concentration < 135 mmol/L, is the most common electrolyte disorder in hospitalized patients [1]. It is often asymptomatic and found incidentally in routine laboratory tests of serum electrolytes. However, it may present with symptoms of increased intracranial pressure such as headache, nausea, and vomiting if the onset is acute or the severity of serum Na^+ lowering is remarkable. Emergency active treatment is necessary when symptoms progress to altered consciousness including confusion, drowsiness, seizures, and coma. However, rapid correction of hyponatremia may be harmful when it is asymptomatic and chronic.

Because serum Na^+ concentration is a function of total body sodium and water, hyponatremia can be caused by an excess of water relative to sodium in the extracellular fluid (ECF). Typically, ECF sodium depletion leads to enhanced renal water reabsorption. This is the simple mechanism of hypovolemic hyponatremia and is characterized by a low level of urine Na^+. Relative hypovolemia, e.g., low effective circulatory volume produced by heart failure or liver cirrhosis, can also enhance renal sodium and water reabsorption and lead to hypervolemic hyponatremia. Essentially, dysnatremia is a water balance disorder caused by water excess or deficit. When the kidney mainly retains water without sodium, euvolemic hyponatremia, such as syndrome of inappropriate antidiuresis (SIAD), ensues. Old age is a common risk factor for hyponatremia because older adults do not excrete water as efficiently as those that are younger [2], probably because of the reduced glomerular filtration rate.

The term SIAD was proposed by Dr. Robertson [3] because plasma vasopressin levels were suppressed in a subgroup of patients who were diagnosed with syndrome of inappropriate antidiuretic hormone secretion (SIADH). A diagnosis of SIADH can be made when unsuppressed levels of arginine vasopressin (AVP) are detected. However, in clinical practice, 'SIADH' is used interchangeably with 'SIAD' because the clinical features are identical and accurate measurement of plasma AVP levels is clinically impractical. The reason why a subset of hyponatremic patients with the SIADH phenotype shows suppressed plasma AVP levels was elucidated partly by Feldman et al. [4]. They described two infants whose clinical and laboratory findings were consistent with SIADH but had undetectable plasma AVP levels because of gain-of-function mutations in the vasopressin V2 receptor (V2R), and coined the term 'nephrogenic syndrome of inappropriate antidiuresis (NSIAD)'. Thus, SIAD caused by renal water retention can be classified into SIADH (with an excess of plasma AVP) and NSIAD (with appropriately suppressed plasma AVP) according to different etiologies [5].

2. Hyponatremia Induced by AVP Analogs

AVP analogs include desmopressin and oxytocin and can induce hyponatremia by acting as V2R agonists. Desmopressin selectively binds the V2R in the kidney and stimulates adenylyl cyclase activity and cAMP production in collecting duct epithelial cells [6]. This enhances osmotic water reabsorption through the upregulation of the aquaporin-2 (AQP2) water channel. Currently, desmopressin not only is used for treating diabetes insipidus but also is prescribed for relieving nocturnal polyuria in older adults. Even low doses of desmopressin can induce hyponatremia in susceptible patients with nocturnal polyuria because an advanced age is an important risk factor for hyponatremia [7]. Compared with AVP, desmopressin has a greater antidiuretic effect because of its longer half-life and selective binding to the V2R [8]. A meta-analysis reported that the incidence of desmopressin-induced hyponatremia was 7.6% in adults with nocturia [9].

Oxytocin may also induce hyponatremia when it is used in obstetrics to induce abortion and to induce or augment labor. Its antidiuretic activity is presumed by the fact that oxytocin and AVP are closely related peptides secreted from the posterior pituitary and that both are nine amino-acid peptide hormones, of which seven are identical [10]. Furthermore, the action of oxytocin as an antidiuretic hormone has been demonstrated in previous studies. Oxytocin increased osmotic water permeability in perfused inner medullary collecting ducts isolated from Sprague Dawley rats [11], and its hydro-osmotic action was mediated by V2R [12]. In Sprague Dawley rats, oxytocin treatment induced apical and basolateral translocation of the AQP2 protein along the collecting duct. This response was blocked by pretreatment with a V2R antagonist [13]. The antidiuretic action of oxytocin was also demonstrated in humans in association with AQP2 upregulation [14]. In brief, pharmacological doses of oxytocin can induce antidiuretic effects as a result of V2R stimulation and subsequent AQP2 upregulation [15].

3. Hyponatremia Induced by Anticancer Chemotherapeutic Agents

Hyponatremia is a common complication in cancer patients because SIAD is potentially caused by malignancies and it can be related to anticancer medical therapy as well. Vincristine, vinblastine, cisplatin, carboplatin, cyclophosphamide, and ifosfamide are the chemotherapeutic agents that are most frequently associated with hyponatremia [16]. Traditionally, these were believed to stimulate AVP release from the pituitary gland or to increase the production of AVP in the hypothalamus. Chemotherapy-induced nausea may be a potential stimulus to AVP secretion [17]. However, evidence supporting AVP hypersecretion induced by chemotherapeutic agents is limited.

Previous studies have shown that SIADH underlies the mechanism of vincristine-associated hyponatremia. A 3-year-old girl who was inadvertently administered an overdose of vincristine developed clinical features compatible with SIADH. Her blood AVP level was more than four times the normal value [18]. In addition, urinary AVP excretion was markedly elevated in a child with acute lymphatic leukemia following the administration of vincristine [19]. Furthermore, animal studies have suggested that SIADH may result from a direct toxic effect of vincristine on the neurohypophysis and the hypothalamic system [20][21].

Cisplatin is a platinum-based chemotherapeutic agent that potentially causes nephrotoxicity. It rarely induces hyponatremia via increasing plasma AVP levels [22]. Moreover, cisplatin nephrotoxicity may produce renal salt wasting causing hypovolemic hyponatremia [23]. Carboplatin may have lesser nephrotoxicity than cisplatin but is rarely associated with hyponatremia [24]. Whether plasma AVP level is increased by carboplatin administration is unclear.

Cyclophosphamide and ifosfamide are representative alkylating agents that may be associated with hyponatremia. Hyponatremia can be induced by various doses of cyclophosphamide during the treatment of malignancy and rheumatologic disease [25]. However, plasma AVP concentrations are not elevated in patients following the administration of intravenous cyclophosphamide [26][27][28]. Furthermore, antidiuresis was reported to occur in response to intravenous cyclophosphamide in patients with central diabetes insipidus [29][30], excluding the possibility of SIADH. This was confirmed by in vitro experiments using primary cultured rat inner medullary collecting duct (IMCD) cells, in which the active metabolite of cyclophosphamide (4-hydroperoxycyclophosphamide) increased cAMP production, AQP2 protein and mRNA expression, and V2R mRNA expression in the absence of vasopressin stimulation [31].

4. Hyponatremia Induced by Psychotropic Agents

Psychotropic agents are a broad category of drugs including antipsychotics and antidepressants used for psychiatric patients, and anticonvulsants are a category of central nervous system-acting drugs for neurologic patients. These three drug classes are the major contributors to drug-induced hyponatremia in current practice. Although they were previously described as inducing SIADH in many case reports [32], a diagnosis of SIAD is more appropriate because plasma AVP levels were undetermined [3]. More specifically, psychotropic agents were recently found to act as V2R agonists and to induce nephrogenic antidiuresis, i.e., NSIAD. In primary cultured rat IMCD cells, they stimulated V2R, increased cAMP production, and led to AQP2 upregulation in the absence of vasopressin [33]. This intrarenal mechanism is reminiscent of chlorpropamide-induced hyponatremia.

Chlorpropamide is a long-acting first-generation sulfonylurea that is no longer used. It was shown to bind to the V2R within the rat renal tubular basolateral membrane in a competitive manner [34] and to increase the V2R density in rat renal papillary membranes [35].

5. Thiazide-Induced Hyponatremia (TIH)

5.1. Clinical Presentation of TIH

Thiazide and thiazide-like diuretics are the common cause of hyponatremia that is usually induced within a few weeks of starting medication but can occur at any time and rapidly in susceptible patients. They are frequently used for the treatment of hypertension and edematous disorders. According to a retrospective cohort study, approximately 3 in 10 patients who exposed to steady use of thiazides develop hyponatremia [36]. Unlike hypokalemia, hyponatremia is dose-independent [37]. Hypertensive old women are particularly at risk of hyponatremia; the major risk factors for TIH are old age, female gender, low body mass, hypokalemia, and concurrent use of other medications that impair free water excretion [38]. Hyponatremia and inability to excrete a water load resolve within 10 to 14 days of drug withdrawal [39].

Serum sodium levels are variable at presentation. Mild hyponatremia, ranging from 125 to 132 mmol/L, is usually asymptomatic, although vague symptoms such as fatigue or nausea are possible [40]. More severe hyponatremia can be asymptomatic or associated with symptoms including headache, vomiting, confusion, dizziness, lethargy, seizures, and even coma. These symptoms of TIH primarily reflect osmotic water shift into brain cells rather than ECF volume depletion [41].

5.2. Pathogenesis of TIH

The mechanisms of TIH are complicated and not fully understood at present. **Table 1** summarizes how thiazides cause hyponatremia from renal and extrarenal mechanisms. Renal mechanisms are primary and derived from the action of thiazides on renal tubules. Extrarenal mechanisms are subsidiary and include insufficient solute intake, polydipsia, and transcellular cation exchange. Low protein intake reduces urea generation and diminishes urine concentration. Patients with TIH may have a higher fluid intake at baseline and during thiazide use than normonatremic individuals [42]. Hypokalemia concurrently induced by thiazide diuretics can also promote hyponatremia. Extracellular Na^+ will enter cells when K^+ exits because of transcellular ion exchange. The renal mechanisms are detailed in the following paragraphs.

Table 1. Mechanisms of thiazide-induced hyponatremia.

Renal (Primary)
NCC inhibition-related
Sodium loss leading to GFR reduction and enhanced proximal tubular fluid reabsorption

Impaired urinary dilution
Independent of NCC inhibition
AQP2 upregulation in the collecting duct
Direct effect
Prostaglandin E2-mediated
Extrarenal (subsidiary)
Insufficient solute intake
Excessive water intake
Coexistent hypokalemia leading to transcellular cation exchange

Thiazides inhibit the Na-Cl cotransporter (NCC) in the distal convoluted tubule, the cortical diluting segment of the nephron. Thus, urine dilution is impaired and water can be retained by thiazides [43]. Similarly, the combination of a thiazide and a K$^+$-sparing diuretic such as amiloride and spironolactone can increase the risk of hyponatremia because of the enhanced urinary loss of sodium in the cortical distal tubule.

Hypovolemic hyponatremia might occur with diuretic therapy because urinary sodium loss leads to a reduction in glomerular filtration rate and enhanced reabsorption of sodium and water in the proximal tubule [47]. Hyperuricemia and low urinary uric acid excretion are characteristic findings of hypovolemia. However, patients with TIH typically show features of SIADH, including low serum uric acid concentrations (<4 mg/dL) and increased fractional excretion of uric acid (>12%) [48]. This suggests exaggerated free water reabsorption or a volume-expanded diluted state [49]. No clinical diagnostic parameters can differentiate TIH from SIAD feasibly [50]. Plasma AVP measurement in patients with TIH has produced conflicting results, with some older studies reporting elevated AVP concentrations [51][52], while more recent studies did not [42][53][54]. Ashraf et al. reported that plasma AVP was undetectable in metolazone-induced hyponatremia [55], suggestive of NSIAD.

On the other hand, Musch and Decaux found that in diuretic-induced hyponatremia, solute depletion was the main causal factor and water retention a secondary one [56]. In seven patients with features of SIADH (e.g., serum uric acid < 4 mg/dL), an infusion of isotonic saline and potassium chloride over 3 days caused cation (Na^+ + K^+) retention (~600 mmoles) and increased the mean serum sodium concentration from 120 mmol/L to 133 mmol/L.

Notably, thiazide-induced renal water retention may be independent of NCC inhibition in the distal convoluted tubule. No hyponatremia is found in Gitelman syndrome or Gitelman-mimic animals carrying a loss-of-function mutation in the NCC regulator Ste20 proline-alanine-rich kinase (SPAK) [49]. Hydrochlorothiazide administration resulted in reduced urine volume in lithium-treated NCC-knockout mice [57]. In particular, thiazides may act directly on the collecting duct, where water permeability is increased by vasopressin-independent mechanisms. César and Magaldi performed in vitro microperfusion of IMCDs from AVP-deficient Brattleboro rats and showed that the addition of hydrochlorothiazide to the perfusate enhanced osmotic water permeability [58]. This effect was attenuated by adding prostaglandin E2 to the perfusate, suggesting that it involved prostaglandin signaling.

Researchers also investigated the antidiuretic mechanism of hydrochlorothiazide in rats with lithium-induced nephrogenic diabetes insipidus (NDI) and found that in association with antidiuresis, hydrochlorothiazide treatment caused a significant partial recovery of AQP2 abundance after lithium-induced downregulation [59].

Certain subpopulations may have a genetic predisposition to the development of TIH. In patients with TIH, hyponatremia was reproducible by single dose thiazide rechallenge where environmental factors such as sodium intake were controlled [53]. Compared with healthy older volunteers, patients with a prior history of TIH had a reduced urinary diluting ability and a greater reduction in serum osmolality [2]. These genetic associations with TIH were supported by the findings of a genetic and phenotyping analysis, suggestive of a role for genetically determined prostaglandin E2-mediated increased water permeability of the collecting ducts in the development of TIH [54]. A subgroup of patients with TIH may carry a variant allele of the prostaglandin transporter *SLCO2A1* gene that leads to a reduced ability to transport prostaglandin E2 across the apical cell membrane in the collecting duct. This reduction in prostaglandin E2 transport leads to increased luminal prostaglandin E2 and activates luminal EP4 receptors, causing membrane trafficking of AQP2 in the absence of AVP and directly enhancing urine concentration and free water absorption [60]. Consistent with this, urinary prostaglandin E2 excretion was elevated in patients with TIH who carried the *SLCO2A1* variant and returned to the control level after cessation of thiazides [54].

However, the role of thiazide diuretics in increasing urinary prostaglandin E2 excretion is not compatible with the previous notion that renal prostaglandins normally protect against TIH [2]. As mentioned above, the microperfusion study by César and Magaldi showed that the addition of prostaglandin E2 counteracts thiazide-induced water reabsorption [57]. Hydrochlorothiazide treatment in lithium-treated NCC-knockout mice reduced urinary prostaglandin E2 levels [56]. Furthermore, clinical studies report that the risk of TIH is increased by the concomitant use of nonsteroidal anti-inflammatory drugs [49][61]. Whether an inhibitor of the prostaglandin EP4 receptor can improve or prevent TIH may answer this controversial issue [62].

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