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Management of Nephrogenic Diabetes Insipidus: An Overview

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Abstract

Diabetes insipidus is a disorder in which the collecting tubules are impermeable to water provoking the excretion of large amounts of diluted urine. In central diabetes insipidus, the release of antidiuretic hormone is decreased, while in nephrogenic diabetes insipidus, the response of the kidneys to this hormone is defective. Common clinical manifestations include polyuria, nocturia, and polydipsia. Laboratory findings show electrolytic imbalance, particularly hypernatremia. Diagnosis can be determined by a hypertonic saline infusion and water deprivation test. In addition to a thorough medical history and physical examination, lab tests and imaging procedures are commonly required. Treatment strategies include diet restrictions, hydration, thiazide diuretics, indomethacin, chlorthalidone, amiloride, and desmopressin. The management of this disorder is facilitated by combining various therapies and considering contraindications to each treatment. However, further studies are necessary to develop safer and more effective medications to manage this complex condition.

Keywords: Diabetes insipidus; Nephrogenic Diabetes insipidus; Central diabetes insipidus

Abbreviations: DI: Diabetes Insipidus, CDI: Central Diabetes Insipidus, NDI: Nephrogenic Diabetes Insipidus, ADH: Antidiuretic Hormone, DCT: Distal Convoluted Tubule, Na: sodium, HCTZ: Hydrochlorothiazide, SLE: Systemic Lupus Erythematosus, ENaC: Epithelial sodium channel, DDAVP: Desmopressin Acetate, NSAID: Nonsteroidal Anti-inflammatory Drug

Introduction

Diabetes insipidus (DI) is a disorder in which the collecting tubules are impermeable to water provoking the excretion of large amounts of diluted urine. Urine concentration dysfunction leads to polyuria and polydipsia [1]. DI is a rare disease with a low prevalence of 3 occurrences per 100,000 people [2]. A neurologic defect in the release of antidiuretic hormone (ADH) is known as central diabetes insipidus (CDI), and nephrogenic diabetes insipidus (NDI) is defined as a defect in the renal responsiveness

to ADH [1]. There are two types of NDI: primary and acquired. An AVPR2 or AQP2 gene mutation causes congenital (primary) NDI. Obstructive uropathy, irregular electrolytes, and specific medicines are all linked to secondary (acquired) NDI [2]. Clinical manifestations of this condition include polyuria, nocturia, and polydipsia [3]. After hypotonic polyuria has been identified, the primary cause must be addressed (primary polydipsia vs. NDI vs. CDI). This can be determined by a hypertonic saline infusion test, water deprivation test, and measures of plasma AVP or plasma copeptin. In addition to a thorough medical history and physical examination, lab tests and imaging procedures are required [4]. When NDI is present, the water deprivation test does not increase plasma sodium, and the rise in urine osmolality following desmopressin administration is < 45% (<300 mosmol/kg) [5]. It can be challenging to manage NDI since only symptomatic treatment is available. Therefore, it is essential to deeply understand all the mechanisms causing NDI to assess a specific and accurate treatment that would be the best for the patient. Patients with NDI who have extrarenal fluid losses frequently require intravenous fluids, decreased dietary solutes, and the use of thiazide diuretics, NSAIDs, amiloride, and/or acetazolamide [6]. In this review study, we aim to provide a comprehensive overview of the different therapeutic options for NDI to help understand the management of this complex condition.

Thiazide Diuretics

Thiazides are diuretics that exert their effect via blockage of the sodium-chloride (Na/Cl) channel in the proximal segment of the distal convoluted tubule (DCT). As a result of blocking the Na/Cl channel, sodium levels are reduced across the luminal membrane, reducing the action of the sodium-potassium pump and decreasing the passage of Na and water into the interstitial space. The method of activation of thiazide diuretics is to cause a change in Na concentration distal to the DCT. Subsequently, ionic channels and pumps work to balance disrupted Na levels. This secondary change to balance Na levels produces many adverse effects [7]. Thiazide diuretics are administered orally as tablets. Generally, the dosage starts at 50 mg daily and may be increased to 100 mg. The dosage should be increased based on individual therapeutic needs [7]. Hydrochlorothiazide (HCTZ) is commonly used alone or in combination with other medications to treat high blood pressure. In addition, it is used to treat edema caused by various medical conditions (i.e., heart, kidney, and liver disease) or by certain medications (i.e., estrogen and corticosteroids) [8].

The adverse reactions of HCTZ include weakness, orthostatic hypotension, pancreatitis, jaundice, nausea/vomiting, sialadenitis, abdominal cramps, gastric irritation, aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia, necrotizing angiitis, pneumonitis, and pulmonary edema. In patients with renal dysfunction, HCTZ can cause electrolyte and/or fluid imbalances, including hypokalemia, hyponatremia, hypercalcemia, and hypomagnesemia. There have been reports of exacerbation of systemic lupus erythematosus (SLE) with hydrochlorothiazide [9,10]. Hydrochlorothiazide is contraindicated in patients with anuria and hypersensitivity to HCTZ or other sulfonamide-derived medications. In pregnancy, this medication is a category B and can be used in cases of generalized edema. Hydrochlorothiazide is excreted in breast milk but is considered to be safe for use during lactation [9].

NSAIDs (Indomethacin)

Indomethacin is an inhibitor of prostaglandin synthesis that decreases the solute delivery to distal tubules, reducing urine output and increasing urine osmolality [10]. After administration, it has a duration of 4-6 hours with an onset of action of 30 minutes. The effective dose is 2 mg/kg/day PO divided every 8 hours [11]. Indomethacin is indicated in patients with streptozocin-induced NDI that persisted after lithium therapy was discontinued [12]. In addition, it can also be given to patients with pain, bursitis, tendinitis, inflammatory and rheumatoid disorders, acute gouty arthritis, and closure of ductus arteriosus in pediatric patients [13]. This medication can impair renal function and have adverse effects such as hyperkalemia, hypernatremia, gastrointestinal bleeding, and elevated creatinine [12,14]. It should be used cautiously in patients with bronchospasm, cardiac disease, congestive heart failure, hypertension, and hepatic or renal impairment [13]. The contraindications for its use include a history of proctitis or recent rectal bleeding, hypersensitivity, preoperative pain associated with coronary artery bypass graft surgery, and history of urticaria, asthma, pregnancy, bleeding disorder, peptic ulcer, stomatitis, ulcerative colitis, and upper gastrointestinal disease [11,13].

Chlorthalidone

Chlorthalidone is a thiazide-like diuretic drug derived from sulfonamides. It is commonly used as a first-line medication for the treatment of patients with hypertension due to its excellent efficacy at the cardiovascular level [15]. Additionally, there is ample scientific evidence to support the use of this medication in other conditions such as nephrolithiasis, generalized edema, chronic kidney disease (CKD), and diabetes insipidus. This drug exerts its therapeutic function by blocking sodium chloride co-transporters in the nephron's distal convoluted tubule (DCT), similar to thiazide diuretics. This prevents the reabsorption of sodium, generating a higher concentration of solute in the lumen of the DCT, causing an osmotic gradient of fluid towards the interior of the tubule. As a result, a higher concentration of sodium and fluid in the tubule increases diuresis. Both increased excretion of sodium and extracellular fluid decreases intravascular water and solute concentration, which corrects the hypernatremia characteristic of NDI patients [16,17].

Chlorthalidone is only available for oral administration, and there is no established dose for use in NDI. However, regimens used in nephrogenic edema are used for NDI (starting from 50 g or 100 mg daily, with a maximum dose of 200 mg/day) [15]. Adverse effects of this medication include gastrointestinal upset, headache, orthostatic hypotension, hypokalemia, hyponatremia,

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hyperglycemia, hyperuricemia, hypersensitivity reaction, and precipitation of crystal-induced arthropathies (i.e., gout, pseudogout). Since electrolyte imbalances are the most common cause of therapeutic failure, monitoring serum electrolytes is essential for patients receiving chlorthalidone periodically [16]. As a sulfonamide derivative, other adverse effects of chlorthalidone include agranulocytosis, aplastic anemia, purpura, necrotizing angiitis, toxic epidermal necrolysis, and pancreatitis. Considering the medication's multiple associated side effects, it should be avoided by patients with any predisposition to present these side effects (i.e., CKD, anuria, gout, hypersensitivity to chlorthalidone or sulfonamides-derived medications, significant electrolyte disorder, pregnancy, syncope, and advanced age) [17,18]. Although chlorthalidone has proven to be an effective diuretic for treating NDI, it has yet to be approved by the FDA for its application in these patients [15]. Therefore, it is necessary to conduct further large-scale prospective studies in order to validate its use in NDI.

Amiloride

Amiloride is a potassium-retaining diuretic and natriuretic. It acts reversibly by blocking luminal epithelial sodium channels (ENaCs) in the late distal tubule and collecting duct. Consequently, reducing sodium influx and decreasing the electrogenic exchange of sodium for potassium and hydrogen, which might cause hyperkalemia and acidosis [19]. The use of amiloride is recommended for patients with chronic hypertension who are also taking diuretics, which are most commonly used to treat heart failure and prevent potassium loss. Patients taking more potent diuretics such as thiazides or loop diuretics may benefit from taking amiloride [20]. Moreover, it has demonstrated clear benefits in preventing and treating coronary events and strokes. The effectiveness of amiloride in resistant hypertension has been shown in recent years, but its potential role in mild to moderate hypertension has not yet been established [21]. A 5mg, 10, 20, 30, 40, and 60mg oral tablet is recommended for adults, and it should be administered with food or meals to prevent gastrointestinal upset [20]. The onset of action of this drug occurs within 2-3 hours, with a peak effect occurring between 6-10 hours after administration and a duration of approximately 24 hours. Absorption ranges from 30% to 90% and can be reduced to 30% when co-administered with food [21].

The use of amiloride is contraindicated in patients with hyperkalemia or hyperkalemia, particularly those with renal impairment, diabetes, or advanced age. The drug should be used with caution if a patient is taking medications that increase potassium as angiotensin-converting enzyme inhibitors. Furthermore, patients with cirrhosis may suffer from imbalances in acid/base, which can result in hepatic encephalopathy. As the kidneys eliminate this drug, patients with renal impairment may be at greater risk of experiencing amiloride-related side effects [20,21].

Desmopressin

Desmopressin acetate (DDAVP) is a synthetic analog of the natural antidiuretic hormone arginine vasopressin, which exerts its effects directly on the V2 receptor and leads to water reabsorption from urine. Consequently, DDAVP is sometimes referred to as an antidiuretic hormone [22]. The drug has a half-life of 6-8 hours and is available in various pharmaceutical formulations, including tablets, intranasal solutions, sublingual preparations, and intravenous forms. The maximum dose required is 0.2 mg orally, 120 ug sublingually, or 10 ug intranasal. The bioavailability of the parental form is up to one hundred times that of the oral form. DDAVP is indicated in diabetes insipidus, enuresis, nocturnal polyuria, and increased mean arterial pressure. One of the major complications is hyponatremia, especially in those patients with continual antidiuretics and alcoholism while continuing average fluids intakes. Hyponatremia can lead to neurological symptoms and cerebral edema [22,23]. In children, desmopressin should be started in a low dose and increased if necessary. Despite limited literature about maturational differences in distribution, metabolism, and excretion, it has been demonstrated that in the pediatric population, the different plasma concentration between adults is up to double the absorption peak [24]. As nephrogenic diabetes insipidus is caused by ADH receptor resistance and not a decrease in ADH levels, DDAVP is not beneficial for this type of DI. In contrast, the administration of desmopressin has been shown to be a safe, effective, and first-line therapy for central diabetes insipidus [25].

Diet and Hydration

Regulation of water intake and elimination in managing diabetes insipidus is crucial for optimal osmotic balance and symptom improvement. Since sodium chloride and dietary proteins in the form of urea account for about 60% of the total urinary osmoles, dietary adjustments directly influence the degree of polyuria in these patients. This relation has been observed in children presenting with polyuria and polydipsia after weaning from breast milk, which has a low sodium and protein content that causes a lesser solute load for the kidneys to excrete [26]. During a study in adults, this was replicated in providing low and high solute concentrations and varying protein amount to patients suffering from DI. In all patients, the increased protein and salt consumption rapidly increased 24-hour urinary osmoles and the volume of urine excreted. In contrast, a reduction in solute and protein load led to a 50-100% decrease in polyuria, respectively [27]. As a result, a low-sodium, low-protein diet plays an essential role in managing DI.

Fluid intake is essential to prevent the harmful effect of repeated episodes of dehydration in nephrogenic diabetes insipidus. Due to the risk of developing highly distended urinary bladders due to polyuria, regular bladder emptying should be indicated to ensure that maximum bladder capacity remains

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within the normal range [28]. For example, infants with diabetes insipidus often cannot drink enough fluids to compensate for urinary losses. In these cases, it is helpful to reduce the intake of sodium in the diet (1 mEq/kg/day) to reduce the solute load. In this population, it is not recommended to reduce protein intake as it can lead to malnutrition [28,29]. The primary strategy for managing NDI is to replace urinary water loss with adequate fluid supply in combination with a low-salt and low-protein diet to minimize obligatory water excretion. NDI standard therapy includes the use of diuretics and nonsteroidal anti-inflammatory drugs (NSAIDs) and can only partially reduce polyuria [29].

Patients with NDI can present with hypernatremic dehydration. First-line rehydration schemes are entirely different from those applied in usual conditions determining a mild to severe hypovolemia dehydration/shock. In NDI, hypernatremic dehydration should always be suspected. Moreover, it is crucial to measure urine output accurately to guide parenteral fluid administration. The standard fluid replenishment includes 5% dextrose in water with an infusion rate that should slightly exceed the urine output [30]. In addition, if the patient is receiving indomethacin, it may be helpful to discontinue its administration until the patient's hydration status has been completely restored to avoid a possible worsening of a prerenal acute renal failure [31].

Conclusion

Diabetes insipidus is a disorder where the collecting tubules are not permeable to water, producing large amounts of diluted urine. In the case of Nephrogenic DI, there is a defect in the renal response to vasopressin/ADH. Management includes the use of different medications, diet, and hydration. Moreover, it can be complex depending on the etiology, patient's age, and pregnancy status. In this review, we found that indomethacin reduces urine output and increases urine osmolality, producing a profound decrease in urinary volume and an increase in urinary osmolality. Amiloride increases urinary sodium excretion and reduces urinary volume and free water clearance. However, this medication is contraindicated in patients with hyperkalemia, renal impairment, diabetes, and the elderly. The use of thiazide diuretics and thiazide-like diuretics can also lead to natriuresis, which will contract the extracellular compartment and decrease the glomerular filtration in the kidney, reducing fluid delivery to the collecting ducts and reducing the urine volume. Desmopressin is particularly useful in central DI as it simulates the action of ADH, leading to water reabsorption from urine. As part of managing diabetes insipidus, regulating water intake and excretion is critical to maintaining optimal osmotic balance and improving symptoms. The primary strategy for addressing NDI is to replace urinary water loss with adequate fluid supply in combination with a low-salt and low-protein diet to minimize water excretion. In summary, the management of this condition is facilitated by a variety of therapies and the consideration of contraindications to each treatment. In spite of the current evidence and the different treatment options available for NDI, further studies are necessary to develop safer and more effective medications for the management of this complex condition.

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