

Diabetes insipidus: The other diabetes

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ABSTRACT

Diabetes insipidus (DI) is a hereditary or acquired condition which disrupts normal life of persons with the condition; disruption is due to increased thirst and passing of large volumes of urine, even at night. A systematic search of literature for DI was carried out using the PubMed database for the purpose of this review. Central DI due to impaired secretion of arginine vasopressin (AVP) could result from traumatic brain injury, surgery, or tumors whereas nephrogenic DI due to failure of the kidney to respond to AVP is usually inherited. The earliest treatment was posterior pituitary extracts containing vasopressin and oxytocin. The synthetic analog of vasopressin, desmopressin has several benefits over vasopressin. Desmopressin was initially available as intranasal preparation, but now the oral tablet and melt formulations have gained significance, with benefits such as ease of administration and stability at room temperature. Other molecules used for treatment include chlorpropamide, carbamazepine, thiazide diuretics, indapamide, clofibrate, indomethacin, and amiloride. However, desmopressin remains the most widely used drug for the treatment of DI. This review covers the physiology of water balance, causes of DI and various treatment modalities available, with a special focus on desmopressin.

Key words: Antidiuretic hormone, desmopressin, polydipsia, polyuria, vasopressin

INTRODUCTION

Diabetes insipidus (DI) is part of a group of hereditary or acquired polyuria and polydipsia diseases. It is associated with inadequate arginine vasopressin (AVP) or antidiuretic hormone (ADH) secretion or renal response to AVP, resulting in hypotonic polyuria and a compensatory/underlying polydipsia.^[1] Polyuria (>50 mL/kg), dilute

urine (osmolality <300 mOsm/L), and increased thirst (water intake of up to 20 L/day) are characteristic of DI.^[2] The kidneys pass large amounts of water irrespective of the body's hydration state.^[3] Untreated DI can cause hypovolemia, dehydration, and electrolyte imbalances.^[4] This article reviews the physiology, causes, and treatment of DI.

REVIEW METHODS

A search of literature on the causes, physiology, and treatment options for DI was carried out using the PubMed database. Only English language articles were included in this review.

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PATHOPHYSIOLOGY OF WATER BALANCE

DI can be caused by two fundamentally different defects: Inadequate/impaired secretion of AVP from the posterior pituitary gland and impaired/insufficient renal response to ADH.^[3] AVP, a neurohypophyseal nonapeptide, regulates body water and osmotic homeostasis.^[5,6] The AVP-neurophysin II gene (*AVP-NPII*) encodes AVP, which is synthesized in the supraoptic and paraventricular nuclei of the hypothalamus as a precursor complex of AVP, NPII, and glycopeptides copeptin and is released as AVP from neurons in the posterior pituitary. AVP and its protein carrier, NPII, are released by calcium-dependent exocytosis.^[6] AVP release may occur due to nonosmotic stimuli also including orthostatic hypotension or emetic reflexes (manifested in nausea and vomiting).^[5]

The AVP system [Figure 1] maintains water balance based on serum osmolality and arterial blood volume via the vasopressin-2-receptor (V2R).^[5-7] AVP activates V2R at the basolateral membrane of the principal cells in the distal convoluted tubule and collecting duct of the kidney. This activates protein kinase A which in turn phosphorylates aquaporin 2 (AQP2) water channels in the intracellular vesicles. Exocytic insertion of AQP2 vesicles into the cell membrane follows, and the collecting duct becomes water permeable, thus concentrating the urine.^[6,7]

EPIDEMIOLOGY OF DIABETES INSIPIDUS

DI is a rare disease, with a prevalence of 1:25,000.^[6] DI can present at any age, and the prevalence is equal among males and females. The age of presentation depends

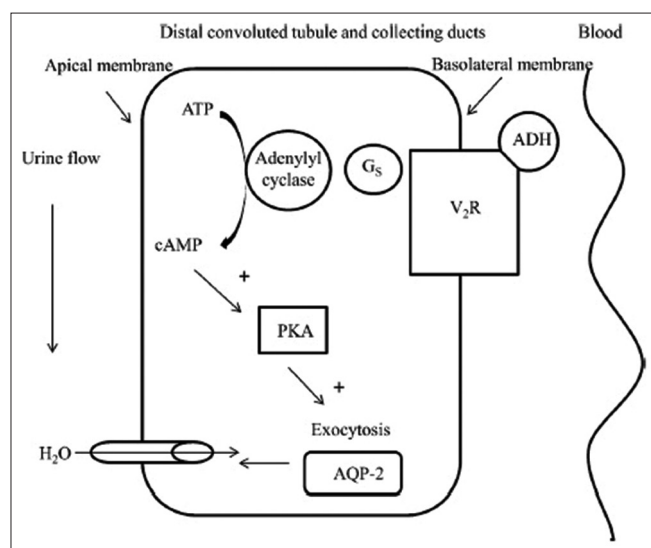


Figure 1: The arginine vasopressin system. cAMP: Cyclic adenosine monophosphate, V2R: Vasopressin-2-receptor, ADH: Antidiuretic hormone, AVP: Arginine vasopressin, Gs: G proteins, PKA: Protein kinase A

on the etiology.^[8] Less than 10% of DI is hereditary. X-linked nephrogenic DI (NDI) accounts for 90% of cases of congenital NDI and occurs with a frequency of 4–8/1 million male live births. Autosomal NDI accounts for approximately 10% of the remaining cases.^[6]

TYPES OF DIABETES INSIPIDUS

Central diabetes insipidus

Central DI (CDI) or neurogenic DI is the most common form of DI, occurring in both the sexes equally and at any age. It is caused by inadequate synthesis/release of AVP, often secondary to surgery or head injury which causes traumatic injury to the hypothalamus or posterior pituitary gland^[3,4] and destruction/degeneration of neurons originating in the supraoptic and paraventricular nuclei of the hypothalamus.^[6] Symptoms of DI manifest after 80–90% of the magnocellular neurons in the hypothalamus are damaged.^[1] Damage to the proximal part of the hypothalamo-neurohypophyseal region kills more neurons than do injuries to the distal region. However, proximal injuries account for 30–40% of posttraumatic and postoperative CDI, while distal injuries account for 50–60% of cases.^[3] The etiology of CDI is summarized in Table 1. Acquired CDI is more common than congenital CDI, and about 25% of adult CDI cases are idiopathic.^[1,6]

Children with acute injury to the nervous system and CDI have a high mortality.^[9] Traumatic brain injury (TBI) is associated with high mortality and acute and

Table 1: Etiology of CDI

Etiology	Contributors
Acquired	
Trauma	Surgery, brain injury
Vascular	Cerebral hemorrhage, infarction, anterior communicating artery aneurysm or ligation, intrahypothalamic injury
Neoplastic	Craniopharyngioma, meningioma, germinoma, pituitary tumor or metastases
Granulomatous	Histiocytosis, sarcoidosis
Infectious	Meningitis, encephalitis
Inflammatory/ autoimmune	Lymphocytic infundibuloneurohypophysitis
Drug-induced or toxin-induced	Ethanol, diphenylhydantoin, snake venom
Other disorders	Hydrocephalus, ventricular/suprasellar cyst, trauma, degenerative diseases
Idiopathic	
Congenital	
Autosomal dominant mutations	AVP-NPII gene mutations
Autosomal recessive mutations	Wolfram syndrome
X-linked recessive mutations	
Idiopathic	

AVP-NPII: Arginine vasopressin-neurophysin II, CDI: Central diabetes insipidus

chronic morbidity. TBI is usually due to road traffic accidents and falls. The direct mechanical impact or the acceleration-deceleration effect of car crashes lead to dysfunction of the hypothalamic-pituitary axis. Trauma may lead to ischemia, hypoxia, alterations of cerebral vascularization/metabolism, and increased intracranial pressure, thus causing pituitary damage.^[10] Among patients admitted to the surgical intensive care unit or level 1 trauma center for severe head injuries, CDI occurred in 12.5% of patients with blunt head injuries and 40.9% of patients with penetrating head injuries. Glasgow Coma Scale ≤ 8 , cerebral edema, and an abbreviated injury score >3 were independently associated with development of CDI. However, CDI itself independently led to an almost 4-fold increase in the risk of death.^[11]

Among Taiwanese children aged 3 months to 18 years, central nervous system (CNS) infection was a common cause of CDI than blunt head injury (35.2% vs. 18.5%), but the development of CDI within the first 2 days of acute CNS injury resulted in a 5-fold higher risk of mortality.^[9] In a larger study, the incidence of CDI after TBI was 18%, and 71.4% of 818 pediatric patients were declared brain dead after CDI diagnosis. A higher mortality was associated with CDI which developed during the first 2 days after head injury.^[12]

Pituitary surgery also results in CDI, with a wide range of incidence (1–67%).^[13] Minimally invasive surgery has a low incidence of postoperative CDI (transient CDI 13.6% and permanent CDI 2.7%).^[14] Abnormalities in the secretion of AVP usually begin during the intraoperative period.^[6] The incidence of immediate postoperative DI was higher among patients undergoing surgery by a traditional method than by the endoscopic transsphenoidal method (36% vs. 15%). The incidence of long-term DI did not vary significantly between the groups.^[15] CDI that developed postoperatively causes 22% of cases in Indian children, and these cases were diagnosed at a later age (6.9 ± 4.7 years) compared to patients with histiocytosis and CNS malformations (3.7 ± 1.5 years and 0.4 ± 0.1 years, respectively). Compared to those with histiocytosis as a cause, more patients with postoperative CDI had a short stature (92.3% vs. 9.1%).^[16]

Tumors have been reported as a cause of CDI, with intracranial tumors accounting for 23% of CDI cases among children and adults in one study.^[17] Tumor-associated CDI was not diagnosed in children aged <5 years.^[18] Germ cell tumors and Langerhans cell histiocytosis (LCH) accounted for 60% of CDI cases in Taiwanese children, and histiocytosis accounted for 18.6% of cases in Indian

children.^[16,19] LCH as a cause of CDI has been associated with better survival.^[17]

Vascular damage to the CNS has been linked to CDI though the pathophysiology is not completely understood. Magnetic resonance imaging (MRI) studies indicated that abnormal blood supply to the posterior pituitary is associated with what is often termed as “idiopathic” CDI.^[1,20] Infections such as cryptococcal meningitis, encephalitis, tuberculosis, tuberculous meningitis, and neurosarcoidosis also contribute to acquired CDI cases.^[21–25]

Congenital CDI is a small contributor in the etiology of CDI. Nonetheless, more than 60 gene mutations in the *AVP-NPII* gene have been identified, most of which are in the *NPII* gene.^[26] In a study of familial CDI, mutations in exon 2 of *AVP* were detected in two Turkish families, but the age of onset differed (<1 year in one family [G45C mutation] and at 4–7 years in another family [C98X mutation]).^[27]

Wolfram or DIDMOAD syndrome (autosomal recessive neurodegenerative disorder resulting in CDI, deafness, optic atrophy, and diabetes mellitus [DM]) is considered a differential diagnosis of CDI that developed in the neonatal period.^[28] Mutations have been detected at nucleotide 997 in exon 8 (A997G) and an insertion in exon 8 of wolframin (WFS1) gene, which results in early-onset CDI in children.^[29] Wolfram syndrome often results in DI and type 1 DM in children. However, an interesting first case of coexistence of CDI and type 2 DM has been reported in a 56-year-old man though no common cause could be determined.^[30]

Nephrogenic diabetes insipidus

NDI results from the failure of the kidney to respond to AVP. Urine production in patients with NDI is typically 12 L/day. Children usually present with the inherited form whereas adults present with the acquired form of NDI [Table 2].^[31] In most cases (90%), inherited NDI is an

Table 2: Etiology of nephrogenic diabetes insipidus

Etiology	Contributors
Acquired	
Drug-induced	Demeclocycline, lithium, cisplatin, methoxyflurane
Infiltrating lesions	Sarcoidosis, amyloidosis, multiple myeloma, Sjogren's disease
Electrolyte imbalance	Hypercalcemia, hypokalemia
Vascular	Sickle cell disease
Congenital	
Autosomal recessive mutations	Mutations in AQP2
X-linked recessive mutations	Mutations in V2R

AQP2: Aquaporin 2, V2R: Vasopressin-2-receptor

X-linked condition caused by a loss-of-function mutation in the *V2R* gene. It is rarely due to mutations in the *AQP2* gene (10%).^[7] *V2R* is predominantly expressed in the distal convoluted tubule and renal collecting tubes, and it responds to AVP thus concentrating the urine.^[7]

In a nationwide survey of NDI patients in Japan, 143/173 patients (82.7%) had congenital NDI whereas the remaining (17.3%) had acquired NDI. Mutations in *V2R* were more common (74.7%) than mutations in *AQP2* (9.2%).^[32] In a study of two unrelated Thai children with NDI, the R181C mutation in *V2R* caused complete NDI whereas the M311V mutation caused mild NDI (*V2R* retained partial activity).^[33]

Drug-induced NDI is most commonly due to lithium, followed by foscarnet and clozapine.^[34] Lithium is used to treat mood disorders and is associated with renal injury including impaired urine-concentrating ability. Lithium enters the collecting duct principal cells predominantly via epithelial sodium channels (ENaC). Excess lithium reduces sodium reabsorption. Lithium inhibits AVP-stimulated translocation of cytoplasmic *AQP2* to the apical membrane, thus delivering hypo-osmotic fluid. Long-term exposure to lithium may down-regulate *AQP2* gene expression.^[35,36] Lithium-induced NDI has been reported in adults and geriatric patients.^[37-39]

Primary polydipsia

Primary polydipsia (PP) results from excessive fluid intake practiced over an extended period. Persons with PP have a defective thirst mechanism or increased the thirst sensation (dipsogenic DI). Patients with an unknown motive for polydipsia are frequently associated with psychiatric disorders (psychogenic polydipsia),^[1] caused by schizophrenia, compulsive behavior, or stress reduction. PP also occurs in psychiatric patients to reduce the effect of anticholinergic drugs.^[40] Phenothiazine administration causes the sensation of a dry mouth and may result in PP.^[4] Excessive fluid consumption resulted in decreased serum osmolality and suppressed release of AVP. Patients exhibit characteristics of DI though pituitary and renal functions are not compromised.^[1] Dipsogenic DI can be caused by chronic meningitis, granulomatous diseases, multiple sclerosis, or other diffuse pathology of the brain.^[41] Cranial MRI is essential to distinguish PP from CDI.^[1]

Gestational diabetes insipidus

Gestational DI occurs in about 1 in 30,000 pregnancies^[42] as a result of degradation of AVP by the enzyme, cysteine aminopeptidase.^[1] Vasopressinase levels are typically higher in pregnant women (up to 300 times higher), more so in twin pregnancies.^[43] However, hormone levels are often normal, suggesting that pregnancy unmasks a

subtle underlying deficiency of AVP.^[1] Gestational DI typically presents in the third trimester^[43] and spontaneously resolves about 2–3 weeks postpartum, but diagnosis to reveal any underlying pathology is necessary.^[1] It is usually underdiagnosed since polyuria during pregnancy is considered normal and does not cause complications.^[44]

Diagnosis of diabetes insipidus

Onset of CDI can be abrupt (due to insult to the body) or gradual (due to tumor or idiopathic causes). The age of onset and the severity of the disease can differ among patients who have congenital disease.^[4,6]

The primary symptoms of DI include persistent polyuria (producing 8–16 L of dilute urine a day) and polydipsia (intake of up to 20 L fluid per day). Other symptoms are dizziness, weakness, nocturia, fatigue, and signs of dehydration (fever, dry skin and mucus membranes, weight loss, poor skin turgor). Hypotension and tachycardia with decreased right atrial and pulmonary artery occlusion pressures and an altered level of consciousness may occur. Young children may present with severe dehydration, vomiting, constipation, fever, irritability, sleep disturbances, retardation of growth, and failure to thrive. Mental retardation can be caused by repeated and unrecognized dehydration.^[4,6]

The diagnostic algorithm of CDI and NDI is described in Figure 2. The ability of the CNS to produce AVP and of the kidney to respond to it is measured by the water deprivation test (Hare-Hickey test) and desmopressin challenge test. A 24-h urine volume is used to confirm polyuria. During water deprivation, hourly measurements of body weight and urine osmolality are made, until 2–3 samples vary by <30 mOsm/kg (or <10%), or until the patient loses 5% of his/her body weight. Serum ADH is then measured and ADH/desmopressin (5 units) is injected. Urine osmolality is measured 30–60 min after this.^[3,6,41] The test is discontinued if the patient loses >5% of his/her body weight and/or plasma Na^+ exceeds 143 mEq/L and/or urine osmolality increases to normal. Response to the administration of desmopressin distinguishes between CDI and NDI. The interpretation of the water deprivation test is described in Table 3.^[6]

Findings suggestive of PP include the history of psychiatric disease, fluctuating symptoms and gradual onset of polydipsia, posterior pituitary bright spot and normal thickness of the pituitary stalk, and hyponatremia after a therapeutic trial with desmopressin.^[1]

New diagnostic markers

Endogenous vasopressin measurement is an important test to differentiate between CDI and NDI. Copeptin (the

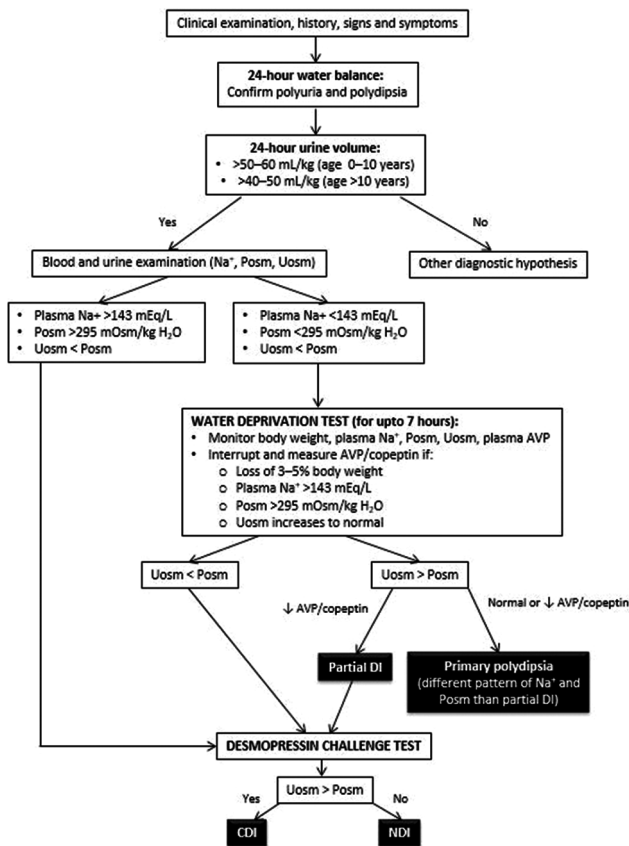


Figure 2: Diagnostic flowchart for central and nephrogenic diabetes insipidus. AVP: Arginine vasopressin, Posm: Plasma osmolality, Uosm: Urine osmolality

C-terminal glycoprotein of the AVP prohormone) can be considered a stable surrogate for endogenous plasma AVP. AVP is unstable, largely attached to platelets and is rapidly cleared. The small size of AVP makes estimation difficult.^[1,45] In one study, copeptin levels were found to be <2.5 pmol/L in all patients with CDI, suggesting that it could be used to distinguish CDI from PP and NDI.^[46]

TREATMENT OF DIABETES INSIPIDUS

Treatment of DI varies for central or nephrogenic forms. The available medications are described in Table 4.

Carbamazepine

Carbamazepine is an anticonvulsant and psychotropic drug used to treat epilepsy or intellectual disabilities. It may stimulate the release of vasopressin from the pituitary gland and act directly on renal tubules. Carbamazepine increased water absorption in the absence of AVP *in vitro*. The effect was cyclic adenosine monophosphate (cAMP)-dependent. In rats, carbamazepine increased water permeability and absorption in the inner medullary collecting duct, acted

Table 3: Interpretation of the water deprivation test and the desmopressin challenge test in the diagnosis of diabetes insipidus

Diagnosis	Urine osmolality (mOsm/kg)	
	After desmopressin	After fluid deprivation
CDI	>750	<300
NDI	<300	<300
PP	-	>750
? partial CDI or ? partial NDI or ? PP	<750	300-750

CDI: Central diabetes insipidus, NDI: Nephrogenic diabetes insipidus, PP: Primary polydipsia, ?: Consider

directly on the V2R-protein G complex and increased *AQP2* expression.^[47] Meinders *et al.*, studied six CDI patients treated with 200–800 mg carbamazepine daily. All patients had a reduction in urinary water output (from 8–16 L/day to 1.9–6 L/day) and an increase in urine osmolality (from 60–120 mOsm/kg to 150–532 mOsm/kg). AVP levels were undetectable in DI patients and healthy subjects, suggesting that carbamazepine did not stimulate the release of, or inhibit the breakdown of AVP.^[48]

Hyponatremia has been detected in 4.8–40% of patients receiving carbamazepine for neurological disorders^[47,49,50] and among patients receiving it for back pain.^[51] Prolonged carbamazepine treatment has been linked to reduction in antidiuretic activity possibly due to auto-induction of carbamazepine.^[52]

Chlorpropamide

The antidiuretic drug, chlorpropamide, decreases the clearance of solute-free water if the neurohypophysis has the residual secretory capacity and normalizes plasma osmolality.^[53] Chlorpropamide administered to children and adults (125–1000 mg daily) reduced urine output from 5.4–10.7 L/day to <2 L/day. Maximal diuresis was achieved in 3–4 days, and the effect was dose-dependent.^[54]

Chlorpropamide may enhance the neurohypophyseal secretion of vasopressin, have a vasopressin-like effect or potentiate the effect of minute amounts of vasopressin which persist in DI.^[54,55] Chlorpropamide may potentiate vasopressin-induced water transport through activation of renal tubular adenylyl cyclase which generates cAMP rather than affecting water movement.^[55]

Clofibrate

Clofibrate is a hypolipidemic agent which stimulates ADH production in patients with partial CDI.^[3,56] Clofibrate treatment (500 mg every 6 h) significantly reduced the mean urine clearance from 280 mL/h to 141 mL/h, and the mean free water clearance from 158 mL/h to

Table 4: Summary of drugs used for the treatment of diabetes insipidus

Drug	Mode of action	Side effects
Carbamazepine	Stimulates the release of vasopressin from the pituitary gland; may act directly on the renal tubules	Hyponatremia
Chlorpropamide	May enhance neurohypophyseal secretion of vasopressin	Hypoglycemia
Clofibrate	Stimulates ADH production in patients with partial CDI	Myopathy
Thiazide diuretics	Inhibits co-transport of Na and Cl, inducing natriuresis	Hypokalemia
Indapamide	Possible proximal tubular water reabsorption	Impairment of renal function, gastrointestinal bleeding, hyperkalemia, hyponatremia and elevated creatinine
Indomethacin	NSAID with antidiuretic activity	Impairment of renal function; severe adverse effects such as gastrointestinal bleeding, hyperkalemia, hyponatremia and elevated creatinine
Amiloride	Blocking of ENaC with amiloride reduces the lithium-induced down-regulation of AQP2 expression and protects the cellular composition of the collecting duct	Hyperkalemia

ADH: Antidiuretic hormone, CDI: Central diabetes insipidus, ENaC: Epithelial sodium channel, AQP2: Aquaporin 2, NSAID: Nonsteroidal anti-inflammatory drug

10 mL/h in 6 cases of DI. Urine osmolality increased from 152 mOsm/kg to 317 mOsm/kg, with a concomitant decrease in urinary ADH excretion in 4/6 patients. There was a significant antidiuretic activity even in patients who were water-loaded.^[56]

Chlorpropamide treatment causes a greater reduction in mean urine volume (59% vs. 47%), and higher urine osmolality compared to clofibrate treatment. However, clofibrate significantly reduces free water clearance. Furthermore, chlorpropamide can cause serious hypoglycemia, unlike clofibrate.^[57] Clofibrate is generally safe, but there have been reports of clofibrate-induced myopathy.^[58] It is likely that hypothyroidism coexisting in patients with secondary DI may precipitate the development of clofibrate-induced myopathy.^[58]

Thiazide diuretics

Thiazide diuretics can be used to treat both NDI and CDI.^[3,59] They act at the distal convoluted tubule and inhibit cotransport of sodium and chloride. Prolonged administration reduces extracellular fluid volume, allowing water and sodium reabsorption at the proximal tubules. Ultimately, there is reduction of urine output.^[59] An animal model of lithium-induced NDI demonstrated that chronic hydrochlorothiazide treatment up-regulates NCC and ENaC, which enhances sodium reabsorption along the distal segments of the nephron.^[60]

Treatment with chlorothiazide (5–10 mg/kg/day) or hydrochlorothiazide (1–2 mg/kg/day) was effective and safe, with hospitalization for hyponatremia required in only 1/13 patients.^[61] Treatment with chlorothiazide or hydrochlorothiazide reduced water intake by 23–40% in children with NDI.^[62] The combination of amiloride and hydrochlorothiazide was superior to hydrochlorothiazide alone and prevented urinary potassium loss, hypokalemia, and alkalosis.^[63] Though hydrochlorothiazide decreases

urine volume by up to 50% in pregnant, the risks of hypokalemia and hypovolemia cause it to be used sparingly in gestational DI.^[43]

Indapamide

Indapamide is an antihypertensive, diuretic drug which could be considered as an alternative drug for mild CDI.^[8] The molecular structure is similar to hydrochlorothiazide and chlorpropamide. As with thiazides, the activity of indapamide may be due to proximal tubular water reabsorption.^[64] The first report on the use of indapamide (at 2.5 mg/day) for DI demonstrated a reduction in the 24-h urinary volume (from 5–16 L to 2.3–9.2 L) in 3 patients with CDI.^[65]

Among patients with treatment-naïve CDI, there was a smaller reduction in mean urine output volume (48.49% ± 10.69% vs. 40.56% ± 9.7%) in patients receiving indapamide compared to those receiving chlorpropamide. Urine osmolality increased in all nine patients receiving indapamide and in 7/11 patients receiving chlorpropamide, while serum osmolality decreased in 4/9 and 7/11 patients, respectively. Chlorpropamide was discontinued due to hypoglycemia in 2 patients while there were no adverse effects among patients receiving indapamide.^[64]

Indomethacin

Indomethacin is a nonsteroidal anti-inflammatory drug which has antidiuretic action.^[4] Weinstock and Moses reported that indomethacin effectively treated NDI that persisted after lithium therapy was discontinued. When used along with desmopressin, there was a marked decrease in polyuria.^[66] A patient who did not respond to desmopressin, thiazides, and amiloride for the treatment of lithium-induced NDI, responded immediately to indomethacin treatment with a reduction in urine volume from 24 L/day to 12 L/day, and ultimately to 2 L/day.^[67] Indomethacin successfully treated streptozocin-induced NDI, with a

rapid correction in polyuria that was independent of the glomerular filtration rate.^[68] Indomethacin may impair renal function^[66] and have severe adverse effects such as gastrointestinal bleeding, hyperkalemia, hypernatremia, and elevated creatinine.^[4]

Amiloride

Amiloride is a diuretic that is useful in the treatment of lithium-induced NDI. It reduces transcellular lithium transport, intracellular lithium concentration and lithium-induced inactivation of GSK-3- β . Blocking of ENaC with amiloride reduces the lithium-induced down-regulation of AQP2 expression and protects the cellular composition of the collecting duct.^[69] In a study of the effect of amiloride versus placebo on lithium-induced NDI, amiloride administered for 6 weeks increased maximal urine osmolality and AQP2 excretion.^[35]

Desmopressin

Vasopressin was first used to treat CDI in 1913, using posterior pituitary extracts containing oxytocin and vasopressin. Pitressin (vasopressin tannate in oil) became available for clinical use in the 1930s and was the principal drug for the treatment of DI almost until the 1970s when desmopressin was introduced. Substitution of the 8th residue of vasopressin with the D-isomer of arginine diminished the pressor effect of vasopressin.^[70,71] This synthetic analog of vasopressin, 1-deamino-8-D-AVP (DDAVP), or desmopressin, has increased and prolonged antidiuretic effect, decreased vasoconstrictive and oxytocic effects, reduced side effects (hyponatremia and convulsions), and enhanced resistance to vasopressinase. It is convenient to administer, being available as an intranasal spray, oral tablet, and orally disintegrating tablet (ODT).^[70-72]

Pharmacokinetics

Desmopressin formulations include intranasal spray, oral tablet, and orally disintegrating tablet (ODT)/oral lyophilisate/melt. Due to safety issues, desmopressin intranasal spray is no longer approved by the United States Food and Drug Administration. This led to withdrawal of the spray and switch to the tablet or melt formulation in a majority of countries; however, the spray continues to be available in India.^[73] The pharmacokinetic properties of oral DDAVP among adult patients with CDI uncontrolled on intranasal DDAVP are described in Table 5.^[74]

The antidiuretic activity of the various formulations is described in Figure 3. The mean urine osmolality at 4 h was only marginally higher for the intranasal compared to the oral formulation. There was no significant difference in the mean urine flow rates for up to 8 h. Increasing the dose

of desmopressin from 200 to 400 mg did not significantly increase the maximal antidiuretic activity.^[74] Among children with CDI, free water clearance decreased rapidly with both

Table 5: Pharmacokinetic properties of the oral and intranasal forms of desmopressin in adults with CDI

	Intranasal desmopressin (20 μ g)	Oral desmopressin (20 μ g)
$t_{1/2z}$	2.2 \pm 0.1	2.0 \pm 0.1
AUC (pmol/L/h)	74.7 \pm 15.0	47.0 \pm 11.6
C_{max} (pmol/L)	24.1 \pm 4.7	15.1 \pm 3.2
t_{max} (min)	40 (20-90)	90 (90-120)

$t_{1/2z}$: Mean elimination half-life, AUC: Area under the curve, C_{max} : Maximum serum concentration, t_{max} : Time at which C_{max} is observed, CDI: Central diabetes insipidus

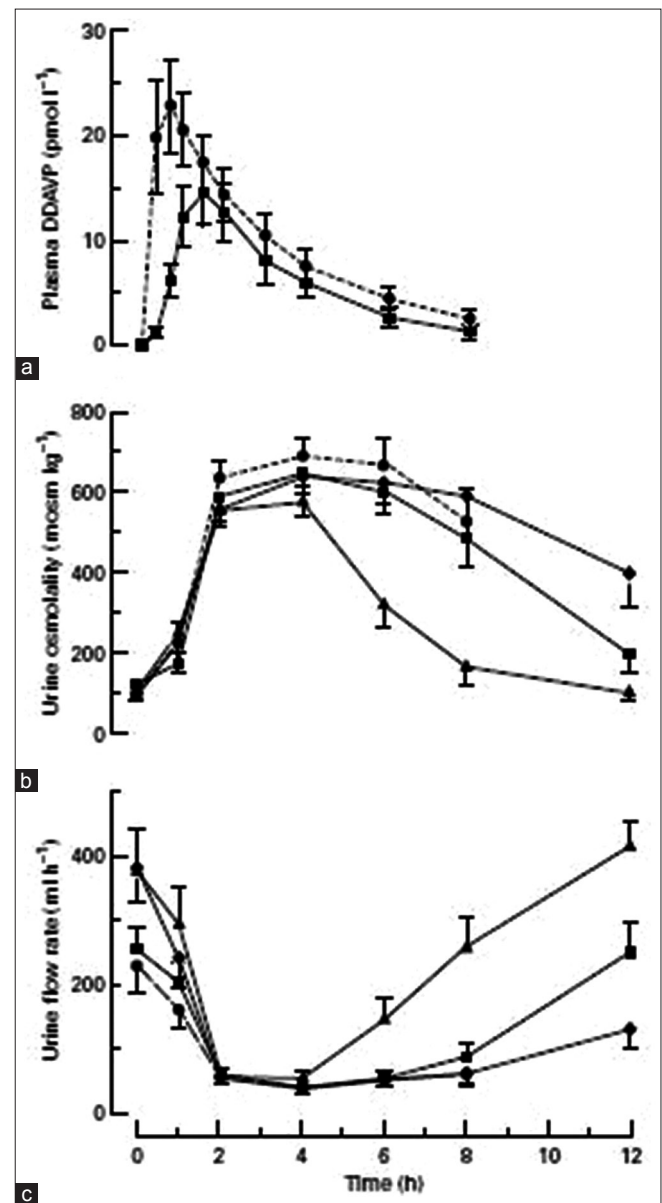


Figure 3: (a) Plasma 1-deamino-8-D-arginine-vasopressin concentrations ($n = 9$), (b) urine osmolality, and (c) urine flow rate at varying intervals after the administration of intranasal or oral desmopressin in 10 adult patients with central diabetes insipidus

intranasal (10–20 µg) and oral (200–400 µg) formulations. Doses of the oral formulation were approximately 20 times greater than those for the nasal formulation.^[75]

Large individual variations in the absorption of orally administered desmopressin have been reported in studies with adults^[74] and children.^[75] In healthy, overhydrated adults who were administered intravenous desmopressin (30–500 ng), the increase in plasma desmopressin and urine osmolality was proportional to the dose. C_{max} occurred at or within 15 min of the end of a 2-h infusion though the individual C_{max} varied over a 2-fold or 3-fold range. Urine osmolality increases were 350 mOsm/kg in the 60 ng group and 700 mOsm/kg in the 500 ng group. The individual variation in time required for a given level of plasma desmopressin to exert its maximum antidiuretic effect could be due to individual differences in the kinetics of one or more intracellular mechanisms that promote the reabsorption of solute-free water by principal cells in renal collecting tubules.^[76]

The gender difference in the activity of desmopressin has been reported in a study of ODT desmopressin for nocturia and among healthy volunteers. At lower doses (25 µg), the decrease in nocturia was larger for women than men. Among patients aged >50 years, women had 2-fold greater decreases in serum sodium levels than men, at doses of 25–50 µg, but a 5-fold greater risk of hyponatremia at 50 µg. Overall, sensitivity to the antidiuretic effect of desmopressin with females was higher than males.^[77]

Oral tablet formulation of desmopressin

Oral tablets have advantages over the intranasal formulation as they can be used easily in infants, elderly patients and patients with visual disturbances and chronic rhinitis. Desmopressin is absorbed unaltered from the gastrointestinal tract after oral administration.^[78] Fukuda *et al.*, studied the use of oral desmopressin (100 µg) in patients with CDI (age 17–36 years) switching from the intranasal formulation. Plasma concentrations of desmopressin peaked (14.7 ± 5.4 pg/mL) at 90 min, and then decreased gradually in the subsequent 3 h. Urine volumes decreased 1 h after administration, with diuretic activity remaining low from 3 h to 6 h after administration. Urine osmolality increased progressively from 1 h after administration, reaching a maximum at 4 h (732 ± 21 mOsm/kg).^[78] Promising results for the oral formulation emerged from a similar study involving a switch from intranasal to oral formulation. Both formulations controlled urine volume (1958 ± 758 vs. 1720 ± 378 mL, respectively) and corrected urine specific gravity to normal (1101 ± 6 vs. 1101 ± 4 , respectively). While the

spray had a more rapid onset of action and a longer duration of action, the tablet was more available and much more easily consumed according to patients ($P = 0.00067$). The dose equivalence ratio for intranasal to 100 µg oral desmopressin was 1:18.^[79]

The long-term use of oral desmopressin has been evaluated. The mean ratio of oral to intranasal doses required to maintain antidiuretic activity was 19 ± 2 (range 15–30). Daily urine volumes were well-maintained (mean volume 1739 ± 68 mL/day, range 1500–1930 mL/day) and urine osmolality was 275–899 mOsm/kg. Importantly, there was no adverse reaction or loss of desmopressin activity over the study period. The oral formulation was as effective as the intranasal formulation in controlling CDI over a 5-year period and was a safe treatment modality.^[78]

A study on oral desmopressin in children with CDI determined that doses of 100–400 µg achieved a mean antidiuretic activity of 8 h. The antidiuretic activity was dose-dependent. The effect on urine osmolality is described in Figure 4. Most patients were discharged from hospital with an initial dose of 100–400 µg thrice daily. The activity of desmopressin correlated with body weight ($r = 0.61$, $P < 0.05$). There were no adverse reactions to any dosage of desmopressin and no significant changes in body weight, blood pressure, or heart rate. During a follow-up period of 6 months, the mean daily oral dose was 550 µg while the mean intranasal dose was 25 µg. Higher initial intranasal doses corresponded to higher oral dose requirements ($r = 0.79$, $P < 0.5$). Oral desmopressin was considered safe and efficacious in the management of CDI in children in the long-term.^[80]

A case of gestational DI was successfully treated with desmopressin (vasopressinase resistant) but not AVP (vasopressinase sensitive). Subcutaneous administration

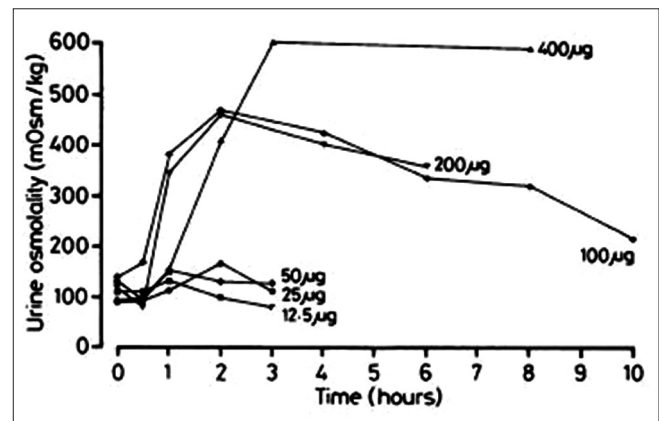


Figure 4: Effect of single rising doses of oral desmopressin on urine osmolality in the seven pediatric patients in the study

resulted in a prompt decrease in oral fluid intake (85 mL/h) and urine output (66 mL/h) and an increase in urine osmolality (656 mOsm/L). Subsequent treatment with intravenous and intranasal forms also controlled the symptoms, and desmopressin was weaned gradually from 6 weeks postpartum while her condition resolved.^[81] A large study in Sweden found that the use of desmopressin during pregnancy was not a risk to infants since the duration of pregnancy and infant birth weight were not affected by the treatment.^[82]

New formulation of desmopressin: Orally disintegrating tablet

The ODT formulation of desmopressin was launched in 2005 for the treatment of nocturnal enuresis. It is a wafer-like formulation which dissolves instantly in the mouth with no need for water,^[70] thus avoiding the ingestion of extra fluids and overcoming difficulties related to swallowing tablets.^[83] It is advantageous over the intranasal formulation which requires cold storage for long-term stability. Absorption of intranasal desmopressin may be erratic due to changes in nasal mucosa due to atrophy, scarring, congestion, or discharge.^[84]

The efficacy of switching to from the intranasal to the ODT formulation was demonstrated in a recent multicenter, open-label, dose-titration study in CDI patients. After 4 weeks of ODT treatment, there was no significant difference between the 24-h urine volume, hourly diuresis rate [Figure 5], urine specific gravity, and urine osmolality compared to the baseline values. More patients had urine osmolality and specific gravity within the normal range [Figure 5c]. Patients received desmopressin ODT 120–360 µg/day in either two or three doses. Treatment-emergent adverse effects were seen in 11 patients, and hyponatremia

was the most common adverse effect. The ratio of ODT to intranasal desmopressin dose was 24. Desmopressin ODT achieved sufficient antidiuretic control compared to intranasal therapy and was well-tolerated over long-term treatment. Individual titration of dosing is important as 6 patients in the study required dose modification due to altered urine volume or sodium levels.^[83]

The ODT formulation was safe and effective in adults with CDI switching from intranasal spray/drops to 60 µg ODT desmopressin. The mean daily dosage of the formulations and the laboratory characteristics are described in Table 6. The ratio of nasal to ODT desmopressin dose was 17.0 ± 7.6 in all patients, 11.7 ± 6.5 in the nasal spray group, and 21.0 ± 5.5 in the nasal drop group. The difference between the ratio for the drop and spray groups was statistically significant. Prior dosage of intranasal desmopressin significantly correlated with the required ODT dose. No events of hyponatremia or water toxicity were reported.^[84]

The potential of desmopressin ODT in very young infants with CDI was recently described. A preterm male infant was administered 60 µg desmopressin ODT, resulting in an

Table 6: Characteristics of the two formulations of desmopressin

	Intranasal desmopressin	ODT desmopressin
Mean dose (µg)	7.76±5.14	104.76±46.3
Serum sodium (mEq/L)	140.5±2.1	139.0±2.7
Plasma osmolality (mOsm/kg)	286.0±5.9	282.7±0.9
Urine osmolality (mOsm/kg)	610±220	663±181

ODT: Orally disintegrating tablet

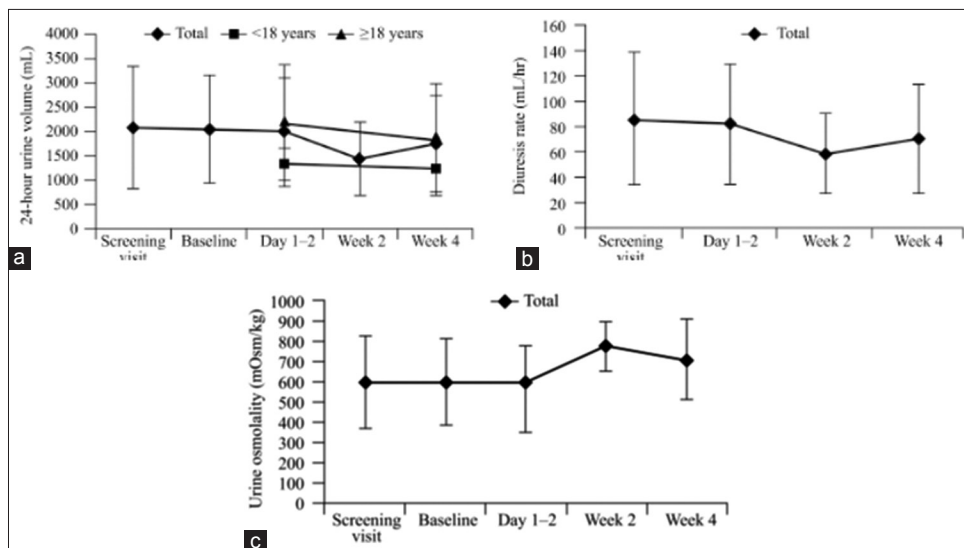


Figure 5: Changes in (a) 24-h urine volume and (b) hourly diuresis rate and (c) urine osmolality over time

increase in urine osmolality within 3 h. The bioavailability of desmopressin was maintained over time, but several dose adjustments were required due to variability in urine output and body weight. After 125 days, 60 µg desmopressin ODT was administered daily, together with a normal fluid intake, resulting in stable random sodium concentrations. In a full-term female infant, 15 µg of desmopressin ODT increased the urine osmolality to > 400 mOsm/kg within 3 h of administration and the effect was maintained for 12 h. By the age of 12 months, DI was managed with 45 µg/day desmopressin ODT.^[70]

Quality of life (QOL) has been assessed using the Peds QL and the Adult Hypopituitarism Questionnaire, but neither is specific for CDI. A new tool, the Nagasaki DI Questionnaire, included 10 questions directly related to CDI symptoms and two questions about the consistency of the effect of and the patient's satisfaction with desmopressin has recently been tested. Patients receiving intranasal spray were either switched to desmopressin ODT or continued the nasal spray. Newly diagnosed patients were treated with desmopressin ODT. The frequency of hyponatremia was lower during ODT than intranasal treatment (13.3% vs. 21.1%), but clinical significance was lacking. Changing from intranasal to ODT desmopressin improved the overall QOL, except the frequency of urination in the daytime. Among patients with newly diagnosed CDI, there were improvements in QOL for each question, without statistical difference.^[85]

Pharmacovigilance data show that hyponatremia is very rare (<1 in 10,000). The lower risk of hyponatremia for the oral formulations makes them preferable over nasal sprays.^[86] The pros and cons of the different formulations of desmopressin are listed in Table 7.

GUIDELINES FOR THE MANAGEMENT OF DIABETES INSIPIDUS

The book, Medicine Update Volume 23, published by the Association of Physicians of India in 2013, had a theme

of "Practical Indian Guidelines and Protocols for all the Common Diseases." It described an algorithm for diagnosis of polyuria [Figure 6].^[41] The Indian Society for Paediatric and Adolescent Endocrinology has enlisted instructions for patients on desmopressin treatment. These include:^[87]

- Never change dosage of medicine without the advice of doctor
- Give next dose of desmopressin only when the effect of the previous day's dose has finished, and the patient begins passing urine frequently for at least 2 h
- On days of cold and stuffy nose, the effectiveness of the desmopressin is low, so the patient will pass larger amount of urine. Give oral fluids according to thirst. Do not try to double the dose of desmopressin

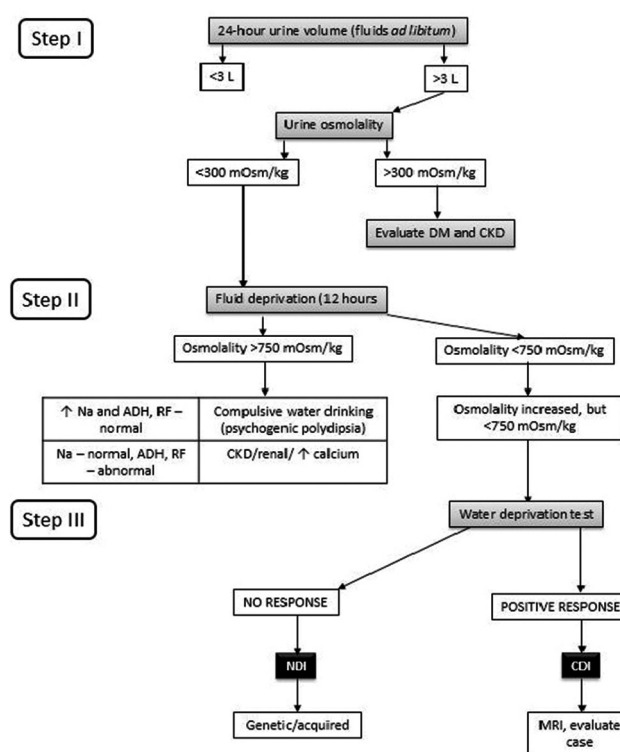


Figure 6: Diagnostic flowchart for polyuria. DM: Diabetes mellitus, CKD: Chronic kidney disease, ADH: Antidiuretic hormone, RF: Renal function, NDI: Nephrogenic diabetes insipidus, CDI: Central diabetes insipidus, MRI: Magnetic resonance imaging

Table 7: Advantages and disadvantages of various formulations of desmopressin

Formulation	Advantage	Disadvantage
Intranasal		Difficult to use in elderly patients, infants, handicapped patients, those with chronic rhinitis
Oral tablet	Stable at room temperature Lower risk of hyponatremia	Requires refrigeration to maintain stability Requires weekly outpatient dose adjustment during the 1 st month of treatment, due to individual pharmacokinetic variations Children may have swallowing difficulties
Orally disintegrating tablet	Easy to administer, especially in children Avoid ingestion of excess fluids Bioavailability is 60% greater than tablets, and it has similar efficacy and safety at lower dosing levels than the tablet	Dose requirement may be high in CDI patients, and dose with melt formulation ranges from 60 to 240 µg

CDI: Central diabetes insipidus

- On days of fever, loose motions, and vomiting, desmopressin should be continued. Extraoral fluids should be given according to thirst
- If the patient becomes unconscious, consult a local doctor immediately.

SUMMARY

DI is a disorder that can be debilitating. It is important to identify the etiology of DI to be able to treat it appropriately. Since its introduction in 1972, desmopressin has been demonstrated as a safe and effective drug for the management of DI in several short-term and long-term studies. Newer preparations including oral and ODT formulations are advantageous over nasal preparations as they are useful in patients who are elderly, mentally, or physically handicapped or have chronic rhinitis. Desmopressin continues to be a valuable drug after more than 35 years since its introduction and provides an effective therapeutic option for DI.

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Conflicts of interest

Dr. Harshad Malve is working as a Lead Medical, Asia Pacific region with Ferring Pharmaceuticals Pvt. Ltd.

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