CASE REPORT

Management of central diabetes insipidus in infancy with low renal solute load formula and chlorothiazide

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Abbreviations

AVP	arginine vasopressin
DDAVP	D-arginine AVP, desmopressin
DI	diabetes insipidus
RSL	renal solute load
S_{na}	serum sodium
S_{osm}	serum osmolality
U_{osm}	urine osmolality

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Diabetes insipidus (DI) refers to the inability to conserve free water and is most commonly caused by hypothalamic/posterior pituitary lesions, resulting in impaired arginine vasopressin (AVP) production and release [1]. Nephrogenic DI results from altered responsiveness to AVP, caused by either mutations in the V2 vasopressin receptor or mutations in aquaporin water channels [1]. With the inability to conserve water, total body water deficits can occur, resulting in hypernatremia, neurologic impairment, and reduced growth [2]. Proper treatment of DI is therefore essential for the wellbeing of the child.

Treatment of central and nephrogenic DI differs. In older children and adults with central DI, antidiuresis can be achieved using synthetic vasopressin analogs, such as D-arginine AVP (DDAVP; desmopressin) [2]. In nephrogenic DI, which is unresponsive to AVP, urine output is reduced by lowering the renal solute load (RSL) and by administering thiazide diuretics that increase urinary osmolality [3,4].

Whereas DDAVP treatment of older children is generally safe and effective, antidiuresis therapy of neonates is complicated by the obligatory high urine output in infancy caused by the consumption of calories in liquid form [5]. Thus, induction of prolonged antidiuresis while the infant drinks can result in water intoxication and hyponatremia [6].

As illustrated by the management of an infant with DI caused by Group B streptococcal meningitis, this report demonstrates the inherent difficulties involved in treating neonatal DI with DDAVP. We also show that using low RSL formula and thiazides to manage central DI in infancy, similar to how children with nephrogenic DI are managed, is simple and effective.

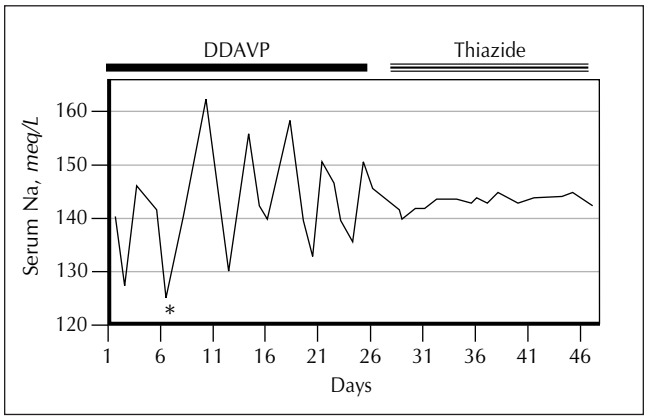
Case presentation

A 2-month-old female presented with a 12-hour history of irritability and fever secondary to Group B streptococcal meningitis. Within 24 hours of presentation she had generalized seizures and was intubated because of deteriorating neurological condition. A head CT scan showed bilateral subdural effusions and multifocal dense lesions that were consistent with cerebral infarctions. After 48 hours of hospitalization, the serum sodium (S_{Na}) rose to 169 meq/L (normal range, 135–145 mEq/L), whereas the simultaneous urinary osmolality (U_{osm}) was 50 mOsm/L (mOsm/kg of water), indicating DI. She was initially managed by replacement of urine output with hypotonic intravenous fluids (5% dextrose solution [D5W] or D5W1/4 normal saline). Intravenous infusions of AVP were started, the urine output dropped, and the U_{osm} increased. After some neurological improvement, the patient was extubated. After AVP infusions were stopped, she continued to have profound DI, with U_{osm} values ranging between 35 and 50 mOsm/L when the S_{Na} exceeded 150 mEq/L.

Because of persistent neurological deficits and poor oral intake, a feeding gastrostomy tube was placed and Similac (Ross Laboratories, Columbus, OH, USA) formula was administered (RSL = 119 mOsm/L; 100–150 mL/kg/d). Urine output remained high and hypernatremia developed. The infant was treated with intranasal DDAVP (0.25 to 1 μg per dose given every 12–24 hrs). Following DDAVP administration, U_{osm} increased to between 500 and 900 mOsm/L and antidiuresis lasted 12 to 36 hours. The patient's response to DDAVP was variable, and consistent eunatremia could not be achieved without episodes of hypo- or hypernatremia (Fig. 1). During one episode of hyponatremia (124 mEq/L), convulsions occurred.

After disappointing results with DDAVP therapy, the formula was changed to Similac PM60/40 (RSL = 92 mOsm/L), and treatment with chlorothiazide (Diuril, Merck & Co., Rahway, NJ, USA; 5 mg/kg, orally, q 12

Figure 1. Changes in S_{Na} values during treatment with either DDAVP (solid bar) or chlorothiazide (open bar) treatment in an infant with central diabetes insipidus



*, seizure. DDAVP, D-arginine AVP (desmopressin).

hours) was begun. On this regimen, U_{osm} increased from 50 to between 110 and 150 mOsm/L urine output dropped by 70%, and S_{Na} values remained between 137 and 147 mOsm/L.

Chart reviews

DDAVP use with central diabetes insipidus

To determine if the problems encountered above in the management of an infant with DI were unique, we examined the medical records of infants treated with DDAVP for central diabetes DI at Yale-New Haven Hospital between 1980 and 2000. This review was approved by the Yale University Human Investigation Committee. Six infants diagnosed with DI in infancy and treated with DDAVP were identified. Causes of DI included holoprosencephaly in two infants, trauma in one, panhyopituitarism in one, and meningitis in two. D-arginine vasopressin was administered intranasally to four infants (0.5–2.5 μg per dose) and subcutaneously to two infants (0.125 μg per dose).

Our review of the medical records indicated that S_{Na} values averaged 141 ± 7 mEq/L (mean ± SEM). Three of six infants had at least one episode of hyponatremia (S_{Na} < 130). All infants had at least one episode of hypernatremia with a S_{Na} > 160 mOsm/L. Three infants required hospitalization for treatment of hypo- or hypernatremia (174–189 mEq/L). There was one death related to a hyponatremic seizure (S_{Na} = 125 mEq/L).

Chlorothiazide use with central diabetes insipidus

In addition to reviewing the records of infants treated with DDAVP, we examined the records of three infants treated with chlorothiazide for central DI. Causes of DI included congenital hypopituitarism, isolated central DI, and meningitis. Generally, 5 mg/kg/d of chlorothiazide was given every 8 to 12 hours. Infants were given low RSL formula (Similac PM60/40) or breast milk. Formula was usually supplemented with free water (20–30 mL for every 120–160 mL of formula).

In these infants, the S_{Na} values averaged 142 plus or minus 2 mEq/L. No infants had episodes of hyponatremia (S_{Na} < 130 mEq/L). One infant had one episode of hypernatremia (S_{Na} = 154 mEq/L). No infants required hospitalization for treatment of hypo- or hypernatremia. Infants were generally maintained on this regimen (6–13 months) until they began to consume solid foods, at which time daily DDAVP therapy was then substituted for chlorothiazide treatment.

Discussion

Water balance

Water is distributed in extracellular (ECF) and intracellular (ICF) fluid compartments that represent about 30% and 40% of total body weight respectively, varying slightly with age [7–9]. Water balance represents net differences between water intake, and urinary plus insensible water losses. In addition to dietary sources, water is generated from the oxidation of foodstuffs (~ 300 mL/m^2/d) [10]. Generally, insensible water losses are 900 mL/m^2/d, and these increase in warm and dry environments and decrease in cool and humid settings [10].

The minimal solute concentration that can be achieved in the urine is about 50 mOsm/L, and the maximum concentration that can be achieved after 2 months of age is 1400 mOsm/L [10,11]. In infants less than 2 months of age, the maximal U_{osm} is about 700 mOsm/L. Depending on dietary intake, minimal and maximal urine volumes will range between 420 and 12,000 mL/m^2/d [10]. In children and adults on normal diets, the average urinary loss is 900 mL/m^2/d [10,12].

In humans, AVP is the key regulator of water homeostasis by promoting renal water reabsorption [1,13]. Arginine vasopressin is produced in the cell bodies of the supraoptic and paraventricular nuclei of the hypothalamus. Axons from these neurons project down the pituitary stalk to the neurohypophysis. Prepropressophysin, the AVP prohormone, is transported down axons to neurosecretatory granules where it is cleaved to form AVP. With increases in serum osmolality or the development of hypovolemia, AVP is released into the circulation.

After its release, AVP binds to multiple receptor subtypes that include V_{1a} and V_2 receptors [14]. The V_{1a} receptor is primarily responsible for AVP-mediated effects on vascular smooth muscle contraction, platelet aggregation, increased factor VIII production, and hepatic glycogenolysis [14]. In contrast, V_2 receptors are expressed in the collecting tubules of the kidneys and

mediate water reabsorption [14]. Activation of V_2 receptor by AVP induces the water channel, aquaporin2, to insert into the luminal membrane of the collecting ducts [14]. Water then moves across these channels and is reabsorbed into the vascular system.

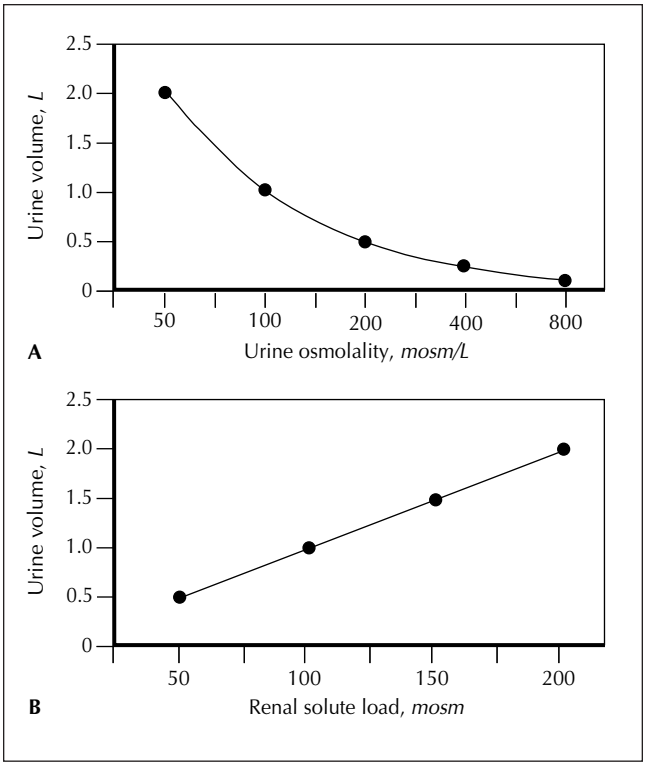
Water balance is exquisitely regulated by changes in AVP levels and thirst. When the effective serum osmolality increases above 285 mOsm/L (S_{Na} 142 mEq/L), AVP secretion progressively increases [1,13]. Changes in U_{osm} are even more pronounced than changes in AVP levels, as the U_{osm} increases exponentially with small increases in AVP levels. Thus, significant water conservation occurs with small elevations in circulating AVP levels making it difficult to achieve partial-antidiuresis using AVP and its analogs.

As an additional means for maintaining water homeostasis, thirst is triggered above a serum osmolality (S_{osm}) of 290 mOsm/L [15]. If there is unrestricted access to free water, even in the presence of untreated DI, normal serum osmolality can be maintained.

In the presence of normal renal function, urine output is dependent on the RSL and urinary osmolality (U_{osm}) (Fig. 2) [7,11,16,17]. Renal solute load includes those substances and minerals that must be filtered and eliminated by the kidney. If the U_{osm} is kept constant, reduction in RSL will lower urine output, whereas increasing RSL will lead to greater urinary losses. Similarly, if the RSL is kept constant, increasing the U_{osm} will reduce urine output, whereas urine output will increase if the U_{osm} falls.

Water conservation largely occurs when U_{osm} increases modestly from the unconcentrated state. As illustrated in Figure 2, much more water is conserved when the U_{osm} rises from 50 to 200 mOsm/L (water conservation increases fourfold) than when the U_{osm} increases from 400 to 800 mOsm/L (water conservation increases twofold).

Figure 2. Change in urine volume as related to either change in urinary osmolality or renal solute load



(A) Change in urine volume as related to change in urinary osmolality, assuming RSL of 100 mOsm/L. (B) Change in urine volume as related to change in the renal solute load, assuming constant U_{osm} of 100 mOsm/L. RSL, renal solute load.

Diabetes insipidus

The diagnosis of DI needs to be considered when the S_{osm} or S_{NA} is elevated and the urine is not concentrated (< 300 mOsm/L) [1,6]. In situations of partial DI, the U_{osm} may reach only 400 to 600 mOsm/L, rather than the expected 900 to 1200 mOsm/L. However, since individuals with partial DI can conserve most of the free-water, they may not be symptomatic [18].

Because of the inability to conserve water, DI is associated with increased urine output. Thus, urine osmolality should be determined in polyuric states. If the U_{osm} is elevated, diabetes mellitus or other conditions associated with an increased RSL should be considered [19]. If the urine is dilute, either central or nephrogenic DI may be present. Primary polydipsia also leads to high urine output and dilute urine. However, these individuals are not hypernatremic, because they do not lose free water, as they can concentrate their urine in hyperosmolar or hypovolemic states.

Most cases of central DI in children are acquired, and tumor, trauma, and infections of the central nervous system are the most common etiologies [20]. Congenital cytomegalovirus, bacterial meningitis, toxoplasmosis, and viral encephalitis have all been shown to cause DI. Tumors of the central nervous system causing DI include craniopharyngiomas, pineal tumors, and pituitary infiltration by leukemia, lymphoma, and histiocytosis-X. Less commonly, central DI may be genetic (Online Mendolian Inheritance in Man Databasae [OMIM] 125700, 192340, 22300).

Diabetes insipidus may result following surgical or other forms of pituitary stalk damage. In this setting, a triphasic response may be seen [21]. Initially there is polyuria, caused by an abrupt cessation of AVP release. This begins 12 to 24 hours after the insult and lasts for 4 to 8 days. An antidiuretic phase, caused by the release of

AVP from the degenerating posterior pituitary, may develop and last 5 to 6 days. Finally, as AVP stores are depleted, DI may return.

Similar to central DI, nephrogenic DI can result in hyperosmolar states and dilute urine. Patients with nephrogenic DI typically present as neonates with X-linked nephrogenic DI (OMIM £304800) caused mutations of the gene encoding the V_2 receptor (chromosome location Xq28) [22,23]. Mutations of the genes that encode aquaporin2 water channels (OMIM £107777) also result in nephrogenic DI. Reflecting the inability to respond to AVP, circulating AVP levels are elevated in nephrogenic DI in hyperosmolar states [24,25].

In addition to genetic forms, hypokalemia, hypercalcemia, lithium, and tetracyclines can cause nephrogenic DI [26]. Hydronephrosis and sickle cell disease also impair the ability to fully concentrate the urine, and isothenuria (fixed U_{osm} = 300 mOsm/L) may be present.

Diagnosis

Diabetes insipidus may be diagnosed when the S_{Na} or S_{osm} is elevated and the urine is inappropriately dilute [1,6]. In situations where the diagnosis is not clear, DI may be distinguished from primary polydipsia by water deprivation testing [27–29]. In the later condition, U_{osm} rises with water restriction, whereas the urine remains dilute with DI [6]. In infants who are dependent on formula for sustenance, water/formula deprivation can be especially trying. Alternatively, double strength formula can be given to increase the RSL and test renal concentrating ability. However, inducing hypernatremia in an infant, either caused by water deprivation or increasing the RSL, may be a risky procedure and requires very close inpatient scrutiny.

If hypernatremia develops and the urine remains dilute, DDAVP may be given to distinguish central from nephrogenic DI. If central DI is present, the U_{osm} typically increases to more than 500 mOsm/L [30]. In contrast, the U_{osm} will remain low in nephrogenic DI. With central DI, central nervous system imaging is indicated and may need to be repeated for several years, as central nervous system lesions that escape early detection may be apparent later [31].

Treatment

In adults and older children, DI can be effectively treated using either AVP or synthetic AVP analogs [1,32]. Aqueous AVP (Pitressin, Parke-Davis, Morris Plains, NJ, USA) has rapid onset and offset of action. After aqueous AVP is administered subcutaneously, prompt antidiuresis is achieved and lasts 4 to 8 hours. Longer acting AVP preparations are also available in the form of Pitressin-tannate in oil (24–48 hours). When precise control of antidiuresis is desired, aqueous AVP may be administered intravenously [33]. In the intensive care unit setting, we have found this approach especially useful, as the onset and offset of action is rapid. However, AVP administration can induce hypertension, reduce intestinal blood flow, and trigger intestinal cramping via activation of V_{1a} receptors. Thus, monitoring of cardiovascular status is needed during AVP use.

Because AVP requires parenteral administration and has side effects, DDAVP is the preferred antidiuretic for treating DI. Replacing the L-arginine in AVP with D-arginine increases the effective half-life and reduces pressor activity [1,25]. The long duration of DDAVP action (12–24 hours) makes the compound especially useful in older patients who consume most of the their calories as solid food, and prolonged antidiuresis is desired. However, because of the prolonged action of DDAVP, water intoxication can occur if there is generous fluid intake during lengthy antidiuresis.

D-arginine AVP preparations are currently available for intranasal, oral, and subcutaneous administration [34]. Intranasal preparations can be administered by either rhinal tube (dose range, 1–10 μg) or by a metered dose spray (10 μg per spray). When infants are treated with DDAVP, diluted preparations of the rhinal tube solutions are often used. Because DDAVP stability is reduced by dilution, these preparations should not be used for more than one week. Intranasal DDAVP doses for children and adolescents range from 2.5 to 10 μg.

Oral DDAVP tablets (0.1 and 0.2 mg) have become recently available in the United States, and, in our experience, are preferred to nasal preparations [2,35]. Although relative potencies vary among individuals, oral DDAVP is 20 to 40-fold less potent than intranasal DDAVP. Oral DDAVP doses range from 50 to 400 μg for children and adolescents.

Subcutaneous DDAVP acetate (4 μg/mL) is advantageous when precise and consistent dosing is needed [36]. Subcutaneous DDAVP is 10-fold more potent than intranasal DDAVP. Thus, subcutaneous DDAVP doses are substantially lower than intranasal (1/10th of intranasal) or oral doses (1/200th of oral).

To achieve antidiuresis for most of the day and night, DDAVP is typically administered in the evening or twice daily. Once-daily doses may also be effective in small children and infants [35].

Special considerations in infants

Infants consume most of their calories as infant formula or breast milk, both of which have low RSLs. To meet caloric needs (110 kcal/kg/d), 166 mL/kg/d (3200

mL/m^2/d) of formula or breast milk are consumed per day, which is equivalent to an adult consuming more than 5 L per day [10,11,37]. To eliminate the large amount of dietary water, the U_{osm} is normally low (100 to 150 mOsm/L) and urine output is high (>5 mL/kg/hr; >2,500 mL/m^2/d in normal circumstances (Fig. 3) [38].

As illustrated by our case and review of the cases of infants treated with DDAVP, infants treated with DDAVP develop water intoxication and hyponatremia when they cannot eliminate their considerable water load [38,39]. This results in the withholding of DDAVP, leading to water loss and hypernatremia. Thus, alternating periods of hyper- and hyponatremia may occur. In addition, variability in the absorption and action of intranasal or oral doses contributes to management difficulties. Use of DDAVP in infants, however, has been reported in a few case reports [40,41].

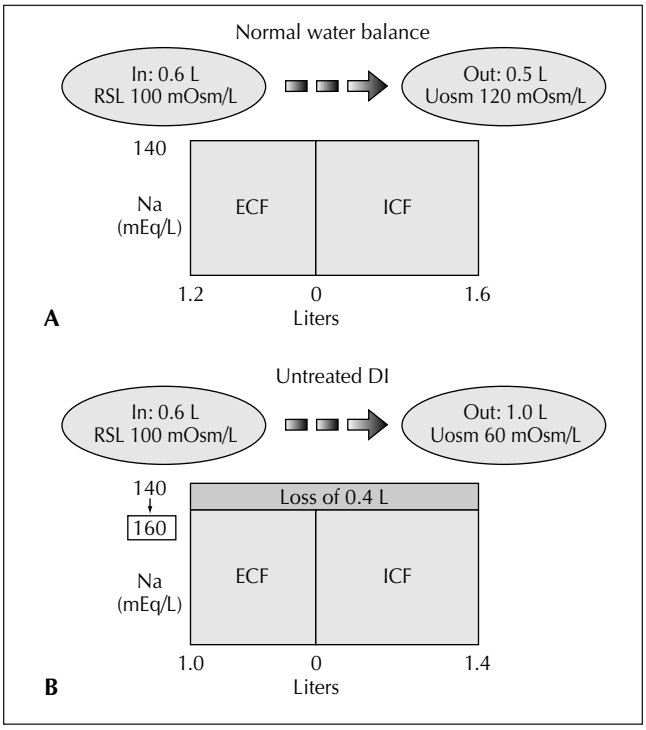
If an infant with DI cannot concentrate the urine even modestly, or the U_{osm} is lower than the RSL concentration of the formula, there will be excessive water loss and hypernatremia (Fig. 3). Yet, if antidiuresis is imposed using DDAVP and fluid intake remains the same, urine output will drop leading to water intoxication and hyponatremia (4A) [6,39]. Thus, alternative approaches that do not utilize DDAVP are needed for the treatment of infants with DI.

One approach is to keep intake and urine output similar and to prevent hyper- or hyponatremia. Standard infant formula can be diluted to one half or two thirds of normal strength with water so that the RSL concentration is less than the maximal U_{osm} (Fig. 4). However, to meet caloric needs, oral intake will need to increase proportionately, which will lead to a high urine output.

As an alternative approach for treating infants with DI who can concentrate their urine to between 70 to 100 mOsm/L, urine output can be reduced and eunatremia achieved using breast milk or Similac PM60/40 (Fig. 4). These preparations have RSLs that are 20 to 30% lower than standard infant formulas, leading to 20 to 30% reductions in urine volume (Table 1). We also give modest water supplementation (30 mL per 120–160 mL of formula). Also, when determining RSL values, please note that renal solute load is distinct from gastric solute load values, which are also available for infant formulas [42].

If the DI is severe (Uosm < 60 mOsm/L), PM60/40 formula must be diluted considerably (one half to two thirds strength) or generous water supplementation given to breastfed babies to compensate for increased free-water losses. However, this also will lead to high urine output. In this setting, adjunctive chlorothiazide therapy is especially

Figure 3. Water balance in a normal infant versus in an infant with diabetes insipidus



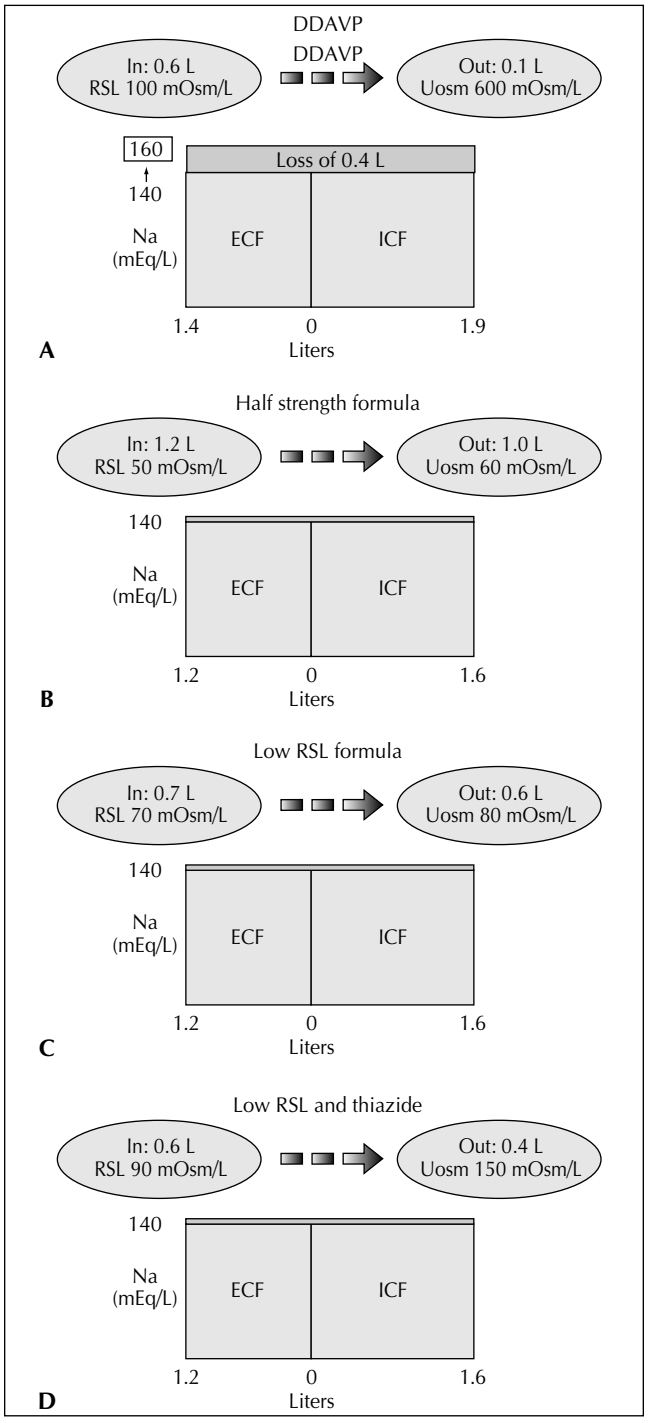
(A) Water balance in a normal 4-kg infant (0.2 m^2). A Darrow-Yannet diagram is depicted showing extracellular (ECF) and intracellular (ICF) fluid compartments [47]. The S_{Na} concentration is shown on the left. Relative fluid compartment volumes are shown below. In this and in other figures, diagrams represent approximations of water balance accounting for insensible water loss (~ 900 mL/m^2/d) and water gained from oxidation of foodstuffs (~ 300 mL/m^2/d), accounting for a net water loss of about 600 mL/m^2/d or approximately 100 mL for a 4-kg infant. (B) Water balance in a 4-kg infant with diabetes insipidus with a U_{osm} of 60 mOsm/L. Excessive urinary water loss results in hypernatremia. DI, diabetes insipidus; ECF, extracellular fluid; ICF, intracellular fluid; IN, volume of formula consumed; Na, sodium; OUT, urine volume; RSL, concentration of the renal solute load of the formula; S_{Na}, serum sodium; U_{osm}, urinary osmolality.

useful in increasing the U_{osm} and reducing urine output [38] (Fig. 4). Although there is no flexibility in the ability to eliminate a water load in patients treated with DDAVP, children treated with thiazides can eliminate excess water, making this form of therapy safer.

At first glance, chlorothiazide use in DI may appear to be counterintuitive, as this compound is used as a diuretic. However, chlorothiazide also interferes with the renal diluting mechanism, leading to increased U_{osm} values [43,44]. Recognition of this important observation of Laragh [43] lead Crawford *et al.* [3,45] to successfully apply thiazide therapy in the treatment of nephrogenic DI.

Similar to treatment for nephrogenic DI [3,45], we generally administer 5 mg/kg of chlorothiazide twice a day and adjust the dose to achieve a Uosm of 100 to 150 mOsm/L. With doubling or tripling of the U_{osm} from baseline, free water output drops to one half or one third

Figure 4. Water balance associated with different treatments of central DI in a 4-kg infant



(A) Overtreatment of neonate with DDAVP while normal feeding occurs results in a gain of free water and hyponatremia. (B) If the U_{osm} is less than 75 mOsm/L, eunatremia can achieved using half- strength formula, or breast milk with considerable water supplementation; urine output will be high. (C) If the U_{osm} is less than 75 mOsm/L, eunatremia can achieved using breast milk or PM60/40 with some water supplementation with modest increases in urine volume. D. If the maximal U_{osm} is less than 60 mOsm/L, eunatremia can be maintained and free water loss reduced using low RSL formula and chlorothiazide. Chlorothiazide increases the U_{osm} facilitating water conservation. DDAVP, D-arginine AVP (desmopressin); ECF, extracellular fluid; ICF, intracellular fluid; Na, sodium; PM60/40, to follow; RSL, renal solute load.

Table 1. Renal solute loads (mOsm/L)

Human milk	75
Similac PM 60/40	92
Enfamil	110
Isomil	126
Nutramigen	130
Cow's milk	230

of the previous rate. As shown by the presented case, when a low RSL formula is combined with chlorothiazide therapy, S_{Na} values can remain normal.

Because thiazide treatment of nephrogenic DI has been shown to be safe and effective [3,4], its utility in treating infants with central DI is not surprising. Thiazide use can be associated with hyperuricemia and hypokalemia; therefore, potassium and uric acid levels need to be monitored. However, these side effects are not generally seen. Other treatments for reducing urine output in nephrogenic DI include amiloride and indomethicin [4,46]. However, there is no reported experience using these agents in treating central DI.

Treatment of older infants with DI

As older infants begin taking solid food, the RSL increases and more water conservation is needed. When infants change from formula or breast milk to cow's milk, the RSL increases nearly threefold, increasing the need for antidiuresis as well (Table 1) [42]. Thus, when patients are taking substantial amounts of solid food (> 9 months; 80% of total calories as solids), they can be managed with DDAVP.

For older infants and children, we are increasingly fond of using oral DDAVP, as reported by others [35]. This may be given as a single or twice daily dose (12.5 to 50 µg/dose). We also have families monitor infant weight, as water overload is associated with weight gain, and weight loss may be indicative of water depletion. If the weight increases by 5% over the previous day, the dose if withheld until diuresis occurs. If the weight drops by 5%, antidiuresis is given along with extra water. As shown in our review of DDAVP treated infants, close vigilance of DDAVP-treated infants with DI is warranted, as life-threatening hypo- and hypernatremia can occur.

Conclusions

Managing DI in infancy using is complicated by the large amounts of formula that infants require to meet caloric needs. Because of this large fluid intake, infants normally produce a "DI-like" urine. Infants are prone to significant water intoxication when antidiuresis is fixed using AVP and its analogs. Consistently normal S_{Na} values are therefore difficult to achieve using DDAVP in infants. In comparison, treating infantile DI with use of low renal solute load formula and chlorothiazide is effective, simple, and has low risks of water intoxication. Our case illustrates the unique aspects of neonatal water

balance that need to be considered to effectively and safely treat DI in infancy. Because of the potential for life-threatening hypo- and hypernatremia, close observation of infants with DI is essential.

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