Treatment of Neurohypophyseal Diabetes Insipidus

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Context: In recent years, there have been several improvements in the treatment of neurohypophyseal diabetes insipidus (DI). They include new formulations of the vasopressin analog, desmopressin; a better understanding of the effect of fluid intake on dosing; and more information about treatments of infants, children, and pregnant women who present special challenges. This review aims to summarize past and current information relative to the safety and efficacy of treatments for the types of DI caused by a primary deficiency of vasopressin.

Evidence Acquisition: The review is based on publications identified primarily by a PubMed search of the international literature without limitations of date.

Evidence Synthesis: In acute settings where fluid intake is determined by factors other than thirst, desmopressin should be given iv in doses that have a short duration of action and can be adjusted quickly in accordance with changes in hydration as indicated by plasma sodium. In ambulatory patients, the oral formulations (tablet or melt) are preferred for their convenience. If fluid intake is regulated normally by the thirst mechanism, the tablets or melt can be taken safely 1 to 3 times a day in doses sufficient to completely eliminate the polyuria. However, if fluid intake consistently exceeds replacement needs as evidenced by the development of hyponatremia, the dose should be reduced to allow higher than normal rates of urine output or intermittent breakthrough diuresis. This regimen is often indicated in infants or children because their rate of fluid intake tends to be greater than in adults. In all cases, the appropriate dose should be determined by titration, owing to considerable interindividual differences in bioavailability and antidiuretic effect.

Conclusions: Desmopressin can provide effective and safe therapy for all patients with neurohypophyseal or gestational DI if given in doses and by a route that takes into account the determinants of fluid intake. **(*J Clin Endocrinol Metab* 98: 3958–3967, 2013)**

Diabetes insipidus (DI) is a syndrome characterized by the excretion of an abnormally large volume of dilute urine (polyuria) and a commensurate increase in fluid intake (polydipsia). It is differentiated into 4 types based on etiology and therapeutic requirements (1, 2).

One type is caused by a deficiency in the production of the antidiuretic hormone, arginine vasopressin. It is variously referred to as neurohypophyseal, pituitary, cranial, or central DI and can result from various diseases or genetic mutations that impair neurohypophyseal function (3, 4) (Table 1). In this type, treatment with vasopressin or an analog such as desmopressin completely eliminates the polyuria, thirst, and polydipsia (2).

DI can also be caused by renal insensitivity to the antidiuretic effect of vasopressin. This type is referred to as nephrogenic DI and can also be acquired or genetic (4, 5). It is refractory to treatment with standard doses of vasopressin or desmopressin but will in some cases respond to

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Abbreviation: DI, diabetes insipidus.

Table 1. Etiology of Diabetes Insipidus and Hypodipsia

- Genetic
  - Autosomal dominant
    - AVP-NPII gene
  - Autosomal recessive
    - AVP-NPII gene
      - Bioinactive AVP
      - Impaired transcription due to large deletion
    - WFS1 gene (Wolfram syndrome)
  - X-linked recessive
    - Unknown gene in Xq28
- Congenital
  - Septo-optic dysplasia
  - Holoprosencephaly
  - Pituitary agenesis
  - Cranial midline defects
- Acquired
  - Cranioencephalic traumatisms
    - Sectioning of the stalk
    - Septic shock
  - Neoplasms
    - Craniopharyngioma
    - Germinoma
    - Pinealoma
    - Optic glioma
    - Pituitary adenoma
    - Leukemia
  - Infiltration/autoimmune
    - Histiocytosis of the cells of Langerhans
    - Lymphocytic hypophysitis
    - Neurosarcoidosis
  - Infections (meningitis/encephalitis)
    - Toxoplasmosis
    - Cytomegalovirus
    - Mycobacterium tuberculosis
    - Listeria monocytogenes
  - Idiopathic
- Nephrogenic DI
- Genetic
  - X-linked recessive
    - V2 receptor gene
  - Autosomal dominant
    - Aquaporin 2 gene
  - Autosomal recessive
    - Aquaporin 2 gene
- Acquired
  - Medication: lithium, cisplatin, amphotericin, demeclocycline, rifampicin, and others
  - Metabolic alterations: hypercalcemia, hypopotassemia, hyperglycemia
  - Renal diseases: amyloidosis, pyelonephritis, renal polycystosis, obstructive uropathies, acute tubular necrosis, falciform anemia
  - Granulomas: sarcoidosis
  - Septo-optic dysplasia
  - Neoplasias: sarcoma
  - Infiltration: amyloidosis
  - Idiopathic
- Primary polydipsia
  - Psychogenic polydipsia or potomania
  - Latrogenic
- Dipsogenic polydipsia
  - Tubeculous meningitis
  - Neurosarcoidosis
  - Head trauma
  - Idiopathic
- Causes of hypodipsia and vasopressin deficiency resulting from destruction of osmoreceptors (86)
- Tumors
  - Craniopharyngioma
  - Pinealoma
  - Meningioma
  - Metastatic
- Granulomas
  - Histiocytosis
  - Sarcoidosis
- Vascular
  - Occlusion of anterior communicating artery
  - Surgical repair of aneurysm
  - Deficiency of protein S
- Head trauma
  - Surgery, especially of craniopharyngioma
  - Accidental
- Other
  - Hydrocephalus
  - Hypogenesis of corpus callosum and other midline structures of brain
  - Cysts
  - Degenerative (Alzheimer's)
  - Idiopathic

supranormal doses of either agonist. For long-term management, however, the only practical way to reduce the polyuria, thirst, and polydipsia is to reduce sodium intake and give a thiazide diuretic, amiloride, or prostaglandin synthetase inhibitors (2, 4).

A third type of DI is due to increased metabolism of vasopressin by an enzyme produced by the placenta (6–8). It is referred to as gestational DI because it usually develops in the second or third trimester of pregnancy and remits spontaneously 4 to 6 weeks postpartum. However, it can also develop immediately after delivery due to massive release of vasopressin from an abruptio placenta (9). Gestational DI is controlled much better with desmopressin than with vasopressin because the analog is resistant to degradation by the placenta (10).

The fourth type of DI is caused by excessive intake of fluids and is usually referred to as primary polydipsia. In this type, vasopressin is synthesized normally, but its secretion is suppressed by excessive fluid intake (11). It is divided into 3 subtypes depending on whether the polydipsia is psychogenic (due to schizophrenia or other cognitive abnormalities), dipsogenic (due to abnormal thirst), or iatrogenic (due to efforts to treat other disorders) (Table 1). Treatment of these patients with vasopressin or desmopressin corrects the polyuria but has little or no effect on the abnormal thirst and/or polydipsia. Consequently, it rapidly and invariably produces water intoxication (hy-

ponatremia) and is strongly contraindicated in this form of DI (12).

Given the markedly different effects of antidiuretic therapy in the 4 types of DI, differentiation between them is essential. This can be difficult by traditional methods because primary deficiencies in vasopressin secretion or action are often partial and, consequently, respond to fluid deprivation tests like patients with primary polydipsia (1). These 3 types of DI can now be differentiated more readily with new techniques that employ assay of plasma vasopressin and/or magnetic resonance imaging of the brain to determine the presence or absence of the posterior pituitary bright spot (4).

The primary purpose of this paper is to provide an updated review of current information on the efficacy and safety of all formulations of the native antidiuretic hormone, vasopressin (Pitressin), and its analog, desmopressin, in the treatment of neurohypophyseal DI. However, other forms of therapy will also be reviewed. The structures of vasopressin and desmopressin are shown in Figure 1. Both produce antidiuresis by stimulating V2 receptors on the principal cells of the kidney (13). High concentrations of vasopressin also stimulate contraction of smooth muscle in the gastrointestinal tract and blood vessels via action at V1 receptors. Desmopressin does not have this effect because it is relatively inactive at V1 receptors (14).

Acute Management of Neurohypophyseal DI

The treatment of neurohypophyseal DI in postoperative or acutely ill patients is straightforward if the patient has a normal thirst mechanism, is able to drink at will, and does not receive fluids for other purposes. In that circumstance, water balance can be maintained just by giving enough antidiuretic therapy to keep urine specific gravity or osmolality near the normal basal level of about 1.015, or 450–600 mOsm/kg. However, if the patient requires iv fluids and/or is otherwise unable to regulate total fluid intake by the thirst mechanism, it may be necessary to continually adjust the level of antidiuresis and/or iv infusion to maintain hydration and plasma sodium within the normal range. In this circumstance, formulations suitable for iv infusion are preferred because they permit the most rapid changes in the level of antidiuresis.

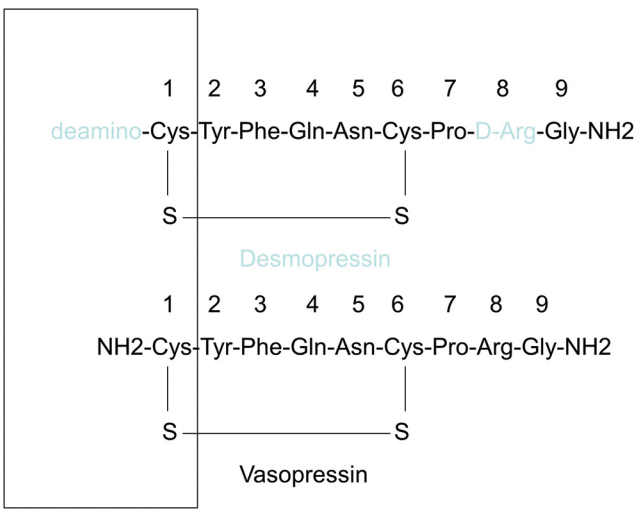

Figure 1. Chemical structure of vasopressin and desmopressin. The box indicates the deamidation of the amino-terminus in desmopressin vs vasopressin.

Vasopressin injectable solution

Vasopressin (Pitressin) has been available for many decades as an aqueous solution of 20 U/mL in a 1-mL vial. Because of its short half-life, (approximately 20 min), some authors recommend that it be given by iv infusion when acute short-term control of antidiuresis is desired (15). For this purpose, it has been suggested that the rate of infusion be started at 0.25 to 1 μU/kg/h and increased every 30 minutes thereafter until a urine specific gravity reaches 1.010 to 1.020 or the rate of urine output falls to around 100 mL/h. Generally, this level of antidiuresis is achieved at an infusion rate of 0.5–3 μU/kg/h. Accidental overdoses resulting from inadequate dilution of the highly concentrated stock solution typically result in severe abdominal cramping, diarrhea, vomiting, and pallor due to action at V1 receptors.

Desmopressin injectable solution

The vasopressin analog desmopressin is also available as a formulation suitable for iv or sc administration. It is supplied in single-dose 1-mL ampoules and multidose 10-mL vials containing 4 μg/mL of the compound. This formulation has been studied and used extensively since the first clinical trial over 40 years ago (16). Early studies showed a definite relationship between the iv dose and the magnitude and duration of the antidiuretic effect (17, 18). In 10 patients with neurohypophyseal DI, a "push" infusion of 1 μg iv increased urine osmolality to a maximum of 700–800 mOsm/kg (18). Further increases in dosage only prolonged the duration of action from an average of 26 hours after 1 μg to 46 hours after 8 μg.

Later studies in more patients revealed large interindividual variability in the magnitude and duration of the antidiuretic response to single iv doses of desmopressin given by "push" infusions (19). This variability was attributed to interindividual differences in renal concentrating capacity because it persisted even when the dose was increased to more than 2 μg (17, 20, 21).

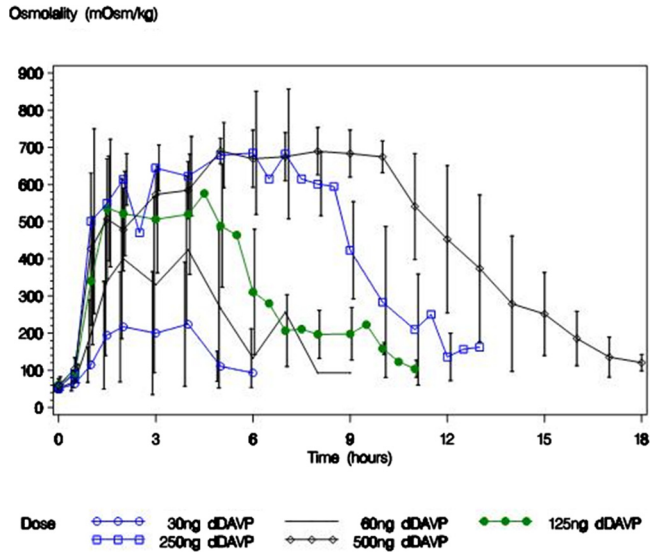

Figure 2. The pharmacodynamic profile of desmopressin, measured as mean urine osmolality (±SD). Based on pharmacodynamic data from 13 neurohypophyseal DI patients receiving desmopressin 30, 60, 125, 250, and 500 ng iv infusions over 2 hours (22). [Reproduced with permission from Springer Science+Business Media.]

A more recent randomized, crossover study in 13 patients with neurohypophyseal DI (22) also showed that the maximum antidiuretic effect and the duration of action tended to vary together as a function of the dose (Figure 2). When infused over 2 hours, a dose of 250 ng increased urine osmolality to an average maximum of about 700 mOsm/kg and reduced urine flow to about 1 mL/min (1.4 L/d). This peak response was nearly identical to that produced by a 4-fold higher dose given by iv push (22), suggesting that the magnitude of the effect depends not only on the total dose but also the rate of rise in plasma desmopressin. This time dependency was also observed in a recent study in water-loaded healthy adults (23). In both settings, the maximum antidiuretic effect produced acutely by a 2-hour iv infusion of desmopressin was considerably less than the maximum achievable in healthy adults during prolonged fluid deprivation (about 1200 mOsm/kg). This lower maximum antidiuretic effect in DI patients around 800–900 mOsm/kg was not due to inadequate levels of plasma desmopressin because doubling the dose from 250 to 500 ng did not increase the maximum antidiuretic effect (Figure 2). It only prolonged the duration of action from an average of about 8 to 11 hours. This finding is consistent with a previous suggestion that the concentrating capacity of the human kidney decreases in the absence of vasopressin and seems to require more than 8 hours of continued stimulation to fully recover (24). It is also clear that there are large individual variations in the magnitude and duration of the initial response to iv desmopressin not only in patients with neurohypophyseal DI (22), but also in water-loaded healthy subjects (23). The cause of this variation is uncertain. It may be due in part to individual differences in the volume of distribution or clearance of desmopressin. Adsorption of desmopressin onto the plastic syringes utilized in the administration could also play a role (25). Other possibilities include individual differences in V2 receptor sensitivity or in the kinetics of the biochemical mechanisms that mediate the antidiuretic effect (23).

Recommendations/precautions

These studies indicate that the parenteral formulation of desmopressin can also be used safely to control neurohypophyseal DI in acutely ill patients. The dose should depend on individual variations in the antidiuretic effect and other factors that determine fluid intake. If the latter is regulated completely by the patient's thirst mechanism, a reasonable approach is to start by giving 250 to 500 ng twice daily via a 2-hour iv infusion and adjust as needed to normalize urine output and maintain plasma sodium within the normal range. However, if the patient is obtunded or requires iv fluid for other reasons, it may be preferable to start with smaller doses of desmopressin (60 to 125 ng iv over 2 h) and adjust them every 3 to 6 hours as needed to reduce polyuria to the extent possible without producing water intoxication (hyponatremia).

Chronic Management of Neurohypophyseal DI

Once established, neurohypophyseal DI rarely remits. The goal of chronic management should be to provide complete, around-the-clock control of the polyuria as conveniently as possible with minimal risk of hyponatremia due to excessive water retention. This goal can usually be achieved by giving a longer-acting form of antidiuretic therapy and educating the patient in the importance of strictly limiting fluid intake to the amounts required to satisfy thirst. Ingesting fluids for any other reason should be avoided because, unlike persons with normal posterior pituitary function, patients receiving long-acting antidiuretic therapy cannot quickly increase their urine output to compensate for an increase of fluid intake. It is also important that the treatment should be dosed so as to not reduce 24-hour urine output below the normal range (15 to 30 mL/kg/d) because it is sometimes difficult to reduce total intake enough to compensate fully for a larger reduction in urine output (26). Finally, it is also essential to be sure that the patient does not have primary polydipsia rather than partial pituitary DI because giving antidiuretic hormone to the former abolishes the polyuria but not the

polydipsia and invariably results in rapid onset of severe hyponatremia (12).

Pitressin tannate in oil

Pitressin tannate in oil is an injectable, long-acting, depot formulation of vasopressin. It was used for many years for long-term management of neurohypophyseal DI (27) but was voluntarily withdrawn from the market by the manufacturer in 1998 and is currently unavailable for this purpose.

Desmopressin nasal spray

Early studies comparing the pharmacodynamic response to iv or intranasal desmopressin in patients with neurohypophyseal DI suggested that the absorption ratio from the nasal mucosa was 10–20% (28). The magnitude and duration of the antidiuretic effect of an intranasal dose varied appreciably between, and even within, patients irrespective of age, severity of polyuria, or body weight (29, 30). Thus, the duration of action ranged from 8 to 24 hours for a 20-μg dose (20, 30, 31) and from 4 to 18 hours after 5 to 10 μg of intranasal desmopressin (32). Using a cutoff for urine osmolality of >400 mOsm/kg, the mean duration of action after 10- and 20-μg intranasal doses was found to be 7 to 9 hours, respectively (33).

Because of its variable absorption and antidiuretic effects, the intranasal formulation has been withdrawn from several markets and in some cases replaced by the more recent oral formulations (34). Nonetheless, the intranasal formulation remains of benefit in many DI patients because the wide range of different strengths allows an individualized administration of the dose required to obtain control of water excretion. Intranasal preparations can be titrated and tailored to the individual need either by rhinyl tube (dose range, 1–10 μg) or by a metered dose spray (2.5–10 μg per spray) (Table 2).

Desmopressin oral formulations—tablets

Peptides, like vasopressin and desmopressin, are in general unsuited to oral administration due to their large molecular size, susceptibility to enzymatic degradation, and short plasma half-life. However, clinical trials in healthy volunteers and patients (35) showed that orally administered desmopressin had a stable antidiuretic effect and a clear dose-response relationship although its bioavailability was low. Thus, desmopressin is also formulated as a tablet (0.1, 0.2, and 0.4 mg) for the treatment of neurohypophyseal DI.

Desmopressin enters plasma 15–30 minutes after oral administration and reaches a maximum concentration after 90 minutes (25). Due to degradation by gastrointestinal peptidases, its bioavailability by the oral route is low (25) (Table 2). The rate and extent of absorption after oral administration is reduced by 40% if taken with food or within 90 minutes of a meal. However, the antidiuretic action of the drug is not affected, at least for the first 3 hours after treatment (36).

Oral administration of desmopressin in doses 10–20 times the intranasal dose provides adequate blood levels of desmopressin to control polyuria in neurohypophyseal DI (Table 2). Due to the ease of administration, oral formulations are the preferred route for the treatment of most patients (35, 37). A total daily maintenance dose of the tablet is normally about 100 to 200 μg 3 times daily, but requirements vary and must be individualized to maintain normal urine output (38). Once-daily doses may be effective in small children and infants (39).

Table 2. Dose Comparison of Different Formulations of Desmopressin

	Melt	Tablets	Spray	Drops	Solution for Injection
Year of introduction	2005	1987	1986, single-dose pipette, multiple-dose spray; 1992, room-temperature stable spray	1972, introduced as rhinyle	1977
Bioavailability	0.25% (95% confidence interval, 0.21–0.31%)	0.16 ± 0.17%	6.00 ± 2.29%	Similar to spray?	N/A
Dose comparison	60 μg 120 μg 240 μg	100 μg 200 μg 400 μg	2.5 μg 5 μg 10 μg	2.5 μg 5 μg 10 μg	N/A <0.5 μg <1 μg

Abbreviation: N/A, not available. The indication of desmopressin is varying between countries and regions, not all desmopressin formulations are approved for the treatment of neurohypophyseal DI in all countries. Based on unpublished bioavailability studies (CS004, RG84063-102, 45A02/48).

Clinical studies of the pharmacokinetics, pharmacodynamics, efficacy, and safety of oral desmopressin tablets have also been conducted in Japanese and Chinese patients with neurohypophyseal DI (40, 41). Both short-term and long-term stable and satisfactory antidiuresis was achieved in most patients tested at total daily maintenance doses of 200 to 600 μg per day subdivided in 2 to 3 doses.

Desmopressin oral formulations—oral melt

Recently, desmopressin has also been developed as a sublingual lyophilisate (melt) formulation containing 60, 120, and 240 μg. This formulation improves the bioavailability of desmopressin by approximately 60% compared to the tablet (42) (Table 2).

The first phase III study of melt in neurohypophyseal DI patients was recently conducted, comparing peroral administration of different doses (60 and 120 μg) of desmopressin melt vs nasal administration (2.5 and 10 μg) (43). In a 4-week multicenter, open-label study, a total of 20 DI patients aged 6–75 years switched from intranasal desmopressin to desmopressin melt with titration to optimal dose over 5 days at the study site. For each patient, optimal dosing in terms of dose and frequency was determined by the investigators based on symptoms such as polydipsia, polyuria, thirst, or clinically significant decreases in serum sodium. At week 4 of treatment, desmopressin melt provided the same level of antidiuretic control (24-h urine volume, osmolarity specific gravity, and hourly diuresis) as intranasal desmopressin at baseline. Desmopressin melt was as efficacious as intranasal desmopressin in both children and adults.

The mean daily dose of intranasal desmopressin given to maintain adequate antidiuresis was not a good predictor of the dose of melt required to obtain the same control (43). The dose ratio averaged 1:24, but individual variation was wide. Thus, individual dose titration is necessary when the formulation is changed. According to current label, dosage should always be adjusted in accordance with the patient's antidiuretic response (44).

Six patients, all adults, developed mild hyponatremia during dose titration of desmopressin melt. However, their sodium returned quickly to normal on continued treatment after a reduction in dose to levels that maintained their urine output within the normal range. One patient experienced serious hyponatremia (124 mmol/L) that led to hospitalization and elimination from the study. This patient, a 63-year-old female, also had secondary adrenal insufficiency treated with 10 mg of cortisol a day.

Other treatments

Carbamazepine, a drug used to treat neurological disorders, also has a significant antidiuretic effect in neurohypophyseal DI (45, 46). At conventional doses of 200 to 800 mg orally, it reduces urine volume by 30 to 90% and increases urine osmolarity proportionately. The mechanism is uncertain. Studies employing immunoassays have shown that carbamazepine reduces plasma vasopressin in healthy subjects (47–49), although in 1 study (47) it impaired urinary dilution in response to a water load. Use of carbamazepine to treat neurological disorders has also been implicated in the development of hyponatremia with inappropriate antidiuresis (50).

Chlorpropamide, a sulfonylurea drug used to lower blood glucose in type 2 diabetes mellitus, also has a significant antidiuretic effect in neurohypophyseal DI. This effect, which was discovered accidentally almost 50 years ago (51), occurs at doses similar to those used in diabetes mellitus (250 to 500 mg orally once a day), reaches a maximum within 3 to 10 days of starting treatment, reduces urine volume by an average of about 60% (range, 30 to 90%) in patients with severe as well as partial deficiencies of vasopressin, and is associated with a proportionate rise in urine osmolarity but no change in solute excretion or glomerular filtration rate (52–69). In patients who do not get satisfactory control of their DI with chlorpropamide therapy alone, the effects can be enhanced considerably by the addition of chlorothiazide (59) or carbamazepine (70). Chlorpropamide also impairs modestly the ability to dilute the urine after water loading not only in patients with neurohypophyseal DI (56, 64–66, 71), but also in most normal subjects (52, 53, 58, 60, 65).

The mechanism of the antidiuretic effect of chlorpropamide in neurohypophyseal DI probably does not involve an increase in vasopressin secretion (69), although it may have this effect in healthy adults (65). Most of the clinical evidence suggests that chlorpropamide acts by potentiating the antidiuretic effect of the very low levels of plasma vasopressin that persist even in patients with severe neurohypophyseal DI (57, 58, 63–65, 72, 73), but a more recent study in LLC-PK cells indicates that chlorpropamide has a direct effect on the V2 receptor (74).

Clofibrate, a drug formerly used to treat certain hyperlipidemias, also has an antidiuretic effect in neurohypophyseal DI (65, 75, 76). Like the other nonpeptide oral agents, the magnitude of the effect varies considerably from patient to patient but, on average, at doses of 2 g/d, it decreases urine volume by about 50% and increases urine osmolarity proportionately. In most patients, combining clofibrate with chlorpropamide does not significantly improve the antidiuretic effect. The mechanism of action of clofibrate is less well defined. It is not associated with an increase in urinary antidiuretic hormone excretion (65), but that finding cannot be interpreted without reference to the change in osmotic stimulation of the hor-

mone. Following these studies, follow-up of long-term clofibrate therapy for hyperlipidemia revealed that it was associated with several serious adverse effects including an unexplained increase in mortality, and clofibrate was withdrawn in 2002.

The thiazide diuretics also have a paradoxical antidiuretic effect in patients with neurohypophyseal DI (77). Unlike the other nonpeptide oral agents, however, they have a similar antidiuretic effect in nephrogenic DI (78). In both cases, the antidiuretic effect tends to be smaller than that produced by the other nonpeptide oral agents, but it is enhanced considerably by restricting sodium intake. Moreover, it potentiates the antidiuretic effect of the other agents and, therefore, is most often used in conjunction with them. Its mechanism of action is not altogether clear. It obviously does not depend on the effect of vasopressin because it works even in patients with severe renal resistance to the hormone (4, 78). The most likely mechanism is decreased reabsorption of sodium in the loop of Henle, resulting in decreased dilution of urine and a reduction in extracellular fluid volume that stimulates a compensatory increase in proximal tubular reabsorption of sodium and water, thereby diminishing delivery of filtrate to the distal nephron and collecting tubules where the defect in urinary concentration exists. The thiazide diuretics impair the ability to excrete a water load and, as a consequence, can produce severe water intoxication with dilutional hyponatremia if given inadvertently to a patient with primary polydipsia (79). As with all other antidiuretic treatments, therefore, accurate diagnosis as to type of DI is essential to safe and effective management.

Special Populations

Neonatal/infants/children

The treatment of neurohypophyseal DI in infants and children differs slightly because their diet contains a proportionally larger quantity of water. Consequently, it may be necessary to allow more urine output to prevent hyponatremia. How much more varies with age and diet and whether the child is allowed to drink water or flavored fluids ad libitum. The general rule should be to eliminate all forms of fluid intake except milk, water, or a set amount of fruit juice and tailor treatment not to urine volume (which is nearly impossible to measure accurately in infants or young children), but rather to fluid intake and/or plasma sodium.

To achieve this goal, desmopressin can be given in different ways. In infants below 12 months of age, the old rhinyl preparation of nasal spray can be diluted 1:10 with physiological saline (33). Oral administration of this dilution once or twice a day in amounts containing 1 to 5 μg of desmopressin provided good control of neurohypophyseal DI, with improved linear growth and weight gain and no signs or symptoms of electrolyte disturbances (80). Subcutaneous injection of the parenteral formulation of desmopressin in doses ranging from 0.02 μg daily to 0.08 μg twice daily is sometimes preferred (81). With this method, serum sodium concentrations varied less, and more remained within the normal range than with intranasal administration. Although studies are limited, case reports indicate that treatment should be initiated with 0.05 μg (0.0125 mL) and then titrated upward according to the effect on diuresis and serum sodium.

In children with neurohypophyseal DI below the age at which they begin to consume solid food and drink spontaneously, brief hospitalization may be worthwhile to determine the dose of desmopressin required to completely eliminate polyuria (82). In these patients, the requisite dose usually ranges from 10 to 20 μg intranasally, 60 to 240 μg of melt, or 100 to 400 μg of the oral tablet. Due to the large individual variation, the dose should start at the lower end and be titrated upward depending on the effect. If intranasal or oral administration is not possible, desmopressin can also be given by injection (1–2 μg sc every 12–24 h). In some previously untreated patients, the maximum effect is not achieved for 24–48 hours after the first dose, probably because the concentrating capacity of the kidney is reduced temporarily by the vasopressin deficiency. It is particularly important to educate children with neurohypophyseal DI and/or their parents about the danger of excessive fluid intake during treatment and make them fully aware of the signs and symptoms of water intoxication.

Pregnancy

Women with pre-existing neurohypophyseal DI who become pregnant and women who develop temporary neurohypophyseal DI during pregnancy (gestational DI) usually can be treated successfully with oral desmopressin. Unlike the native hormone, the analog is resistant to degradation by leucine aminopeptidase produced by the placenta (10, 83). The doses required are similar to or slightly greater than those required in the nongravid state and, in the case of gestational DI, they can be discontinued 4 to 6 weeks after delivery when the DI and blood levels of the peptidase usually disappear. The only other difference in management is that, in monitoring the effect of treatment, it should be remembered that the plasma sodium concentration during pregnancy is normally about 5 mOsm/kg lower than in the nongravid state. Desmopressin can be administered postpartum to nursing mothers because very little appears in breast milk (84). Some cases of gestational

DI may be resistant to treatment with desmopressin as well as vasopressin owing either to abnormally high levels of vasopressinase or some defect in the kidneys.

Elderly

Treatment of neurohypophyseal DI is usually lifelong because recovery from an established vasopressin deficiency is uncommon, even if the underlying cause is eliminated (85). The management of neurohypophyseal DI in the elderly is similar to that in young adults, but the risks of developing hyponatremia may be greater at least when intranasal desmopressin is used (82). The reason is unclear but may relate to increased renal sensitivity to desmopressin or, more likely, abnormalities in the osmoregulation of thirst and fluid intake, which are known to occur in the elderly.

Hypodipsia with neurohypophyseal DI

A few patients with neurohypophyseal DI also have a deficiency in thirst (hypodipsia) due to a variety of disorders that damage the osmoreceptors in the anterior hypothalamus (Table 1) (86). The management of these patients is extremely challenging because they have lost both of the homeostatic mechanisms that normally regulate water balance. Consequently, they tend to suffer from wide swings in plasma sodium from hyper- to hyponatremia, even when their DI is well controlled (86). These swings cannot be prevented by prescribing a fixed level of fluid intake because insensible and even urinary losses of water vary significantly from day to day depending on temperature, activity, and diet. Consequently, it is necessary to prescribe fluid intake on a sliding scale based on daily changes in weight and/or plasma sodium (86, 87). Because the frequency and severity of the hypernatremia are increased by water loss, complete around-the-clock control of their DI is of greater importance than in patients with a normal thirst mechanism. Such control can be achieved with desmopressin or with chlorpropamide, alone or in combination with chlorothiazide. In some respects the latter may be preferred because the level of control tends to be more stable and chlorpropamide may also stimulate thirst (88).

Summary

The treatment of choice for long-term management of neurohypophyseal DI is desmopressin tablet or melt. When dose titrated to allow for individual differences in bioavailability and renal sensitivity, either formulation completely eliminates the polyuria, thirst, and polydipsia that characterize the disorder. The risk of hyponatremia during such treatment is uncertain but appears to be modest (<5%), at least if urine volume is reduced no more than to the normal basal range and patients with primary polydipsia are accurately differentiated from those with partial pituitary DI. When started on treatment, the patient should also be educated about the need to drink no more than necessary to satisfy thirst. Compliance with this requirement can be problematic in infants, children, and adolescents whose fluid intake is often motivated by factors other than thirst. Accurate data on the incidence of hyponatremia and the factors that influence it during long-term therapy of neurohypophyseal DI are needed.

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