



MODERN APPROACH IN TREATMENT OF DIABETES INSIPIDUS

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ABSTRACT

In this paper we have reviewed the position of desmopressin in the treatment of diabetes insipidus. Desmopressin is a synthetic analog of vasopressin, with more pronounced antidiuretic effect. It is treatment of choice in substitution therapy of diabetes insipidus. Its application before sleeping time can reduce nocturnal enuresis, so it has a place in the treatment of *enuresis nocturna*. Antidiuretic effect of desmopressin is the result of agonistic effect on V₂ receptors in the renal tubules. The efficacy and safety of desmopressin in mentioned indications was confirmed in clinical studies.

KEY WORDS: desmopressin, diabetes insipidus

INTRODUCTION

Desmopressin is a synthetic vasopressin analog, with enhanced effect and longer duration of action than vasopressin or lyspressin (lizine-vasopressin). Desmopressin differs from naturally-occurring vasopressin by deaminated hemicystein at position 1 and substituted D-arginine for L-arginine at position 8. This has been shown to diminish vasopressor activity, enhance antidiuretic-to-pressor potency, and prolong the duration of action of the compound. Vasopressin, hormone of neurohypophysis, is released when the plasma osmolarity is increased and/or blood pressure reduced. Diabetes insipidus, as a consequence of vasopressin deficit, is characterized with reduced reabsorption of water from collecting tubules of the kidney and patients suffer from polydipsia and polyuria (1).

PHARMACODYNAMIC CHARACTERISTICS

Desmopressin was synthesized in 1967, and from 1974 is widely used in treatment of diabetes insipidus. Neurohypophysis hormones, vasopressin and oxytocine, are released from endings of neurosecretore neurons which somas are located in paraventricular and supraoptic nuclei of hypothalamus. Vasopressin is released when the plasma osmolarity is increasing and/or blood pressure dropping. The actions of vasopressin are mediated through interaction with two types of receptors, V1 and V2. Vasopressin acts on V2 receptors, enhances generation of cyclic AMP in collecting tubules of the kidney and increases reabsorption of water according to the osmotic gradient. That is the essence of its antidiuretic effect. Diabetes insipidus, as a consequence of vasopressin deficit, is characterized with reduced reabsorption of water from collecting tubules of the kidney and patients suffer from polydipsia and polyuria. Desmopressin is a drug of choice in the treatment of diabetes insipidus. Desmopressin is used in management of nocturnal enuresis. Desmopressin given at bedtime to patients with nocturnal polyuria was associated with reduced nocturnal diuresis. With naturally occurring vasopressin (arginine vasopressin) the antidiuretic-to-pressor ratio is 1 (approximately 400 units/mg). Antidiuretic-to-pressor potency of desmopressin is 2000 to 4000:1 and the duration of action ranges from 6 to 24 hours. This is considerably longer than the duration of action for arginine vasopressin (2 to 6 hours). The prolonged duration of action of desmopressin as compared to arginine vasopressin is most likely due to resistance to enzymatic

cleavage, delayed absorption from nasal mucosa, and enhanced generation of cyclic AMP in the renal medulla (1). In addition, desmopressin may be useful in the treatment of some coagulopathies, hemophilia A and von Willebrand's disease (2). Desmopressin significantly shortens bleeding time in healthy volunteers treated with aspirin in the duration of up to 4 hours. Evaluation of dose and effect ratio in patients with diabetes insipidus has shown that oral doses of desmopressin ranging from 0,025 milligrams to 0.4 milligrams induce significant antidiuretic effects. Desmopressin in dosage range from 0.1 to 0.2 milligrams per day has the optimal antidiuretic effect in the most patients with duration of 8 hours. In doses of 0.4 milligrams antidiuretic effect lasts for 12 hours. With increasing oral dosages the concentration of desmopressin in plasma is increasing in dose-dependent manner (3). In a study of patients with nocturnal enuresis, patients who were classified as responders to desmopressin therapy experienced increased fractional excretion of sodium at night compared to those classified as non-responders and a group of normal control subjects (4). A lack of circadian variation in the plasma osmolality was observed in both responder group and non-responder group. Normals and responders experienced a steady increase in plasma potassium during the night. Plasma sodium was stable without circadian rhythm in all three groups. Desmopressin responders did not experience significant fluctuation in diurnal variation of plasma vasopressin values but the other two groups did experience significant increases peaking at 05:00 hours ($p \leq 0,05$). Only normal control patients experienced significant circadian variations in plasma atrial natriuretic peptide levels ($p < 0,001$). Patients with complete form of diabetes insipidus experienced significant decrease in plasma triglyceride levels following desmopressin therapy ($p = 0,027$). However, similarly treated patients with partial diabetes insipidus did not experience significant change in triglyceride levels. Favorable effects of desmopressin on lipid and lipoprotein metabolism in complete diabetes insipidus patients may be due to either direct effects or through modifications of factors that contribute to lipid metabolism (5).

MECHANISM OF ACTION

Desmopressin increases reabsorption of water in collecting tubules of the kidney. Desmopressin, also, stimulates factor VIII and plasminogen activated release. Antidiuretic effect is the result of agonistic activity on V2 receptors placed in tubules of the kidney. This effect is the result of enhanced reabsorption of water, probably

based on opening of pores and channels which play role in water reabsorption according to the osmotic gradient. Molecular mechanisms of action include stimulation of adenylate cyclase and enhanced synthesis of cAMP. Vasopressin-2 receptors are also placed extrarenally, and play role in factor VIII release. Desmopressin has minimal effect on V₁ receptors that are located in smooth muscles of blood vessels walls and numerous different organs (1)

PHARMACOKINETIC CHARACTERISTICS

Desmopressin is absorbed in nasal mucosa. Bioavailability of desmopressin after intranasal administration is 3,3% to 4,1% compared to intravenous or subcutaneous administration (1). After oral administration, large part of desmopressin dose is degraded in gastro intestinal tract, but after high doses there absorption is sufficient for the therapeutic effect (6). After oral administration bioavailability is 5% compared to intranasal administration, and 0,16% compared to intravenous administration. Maximal concentration in plasma and AUC do not increase proportionally to administrated doses. Regardless of administrated doses, plasma half-life of desmopressin is 1,5 to 2,5 hours (3). Terminal plasma half-life of desmopressin is 4 to 5 hours (7). Distribution half-life of intranasal desmopressin is 7,8 minutes. Desmopressin does not penetrate hemato-encephalic barrier. Volume of desmopressin distribution is 0,2 to 0,3 L/kg. *In vitro* studies using human liver microsomes showed that desmopressin was not metabolized by liver. Desmopressin is almost completely excreted in urine. Elimination half-life after intranasal administration is 0,4 to 4,0 hours.

INDICATIONES AND DOSAGE

Desmopressin is used in the treatment of neurohypophyseal diabetes insipidus, *enuresis nocturna primaria*, nocturia associated with nocturnal polyuria in adults and in testing of renal function capacity. Also, it is used in management of mild-to-moderate hemophilia A or mild-to-moderate type I von Willebrand's disease. Formulated as nasal spray, desmopressin is used in crises prevention of sickle-cell anemia by inducing hyponatremia. In patients with uremia, desmopressin reduces bleeding time by rising concentration of factor VIII. Desmopressin dosage should be individualized. Doses are titrated according to the patient's responses and pharmaceutical formulation of desmopressin. The food can reduce intensity and duration of desmopressin small doses antidiuretic effect.

PRECAUTIONS

Drugs which are releasing antidiuretic hormone (tricyclic antidepressives, chlorpromazine, and carbamazepine) can cause additional antidiuretic effect with increased risk of fluid retention. Nonsteroidal anti-inflammatory drugs can cause fluid retention and hyponatremia. Loperamide can increase concentration of desmopressin in plasma as well as the risk of fluid retention and hyponatremia. Concomitant desmopressin and glyburide therapy has resulted in inhibition of desmopressin's effects and decreased antidiuretic effect (13). Concomitant desmopressin and dimeticon therapy can reduce desmopressin absorption. The food can reduce intensity and duration of desmopressin small doses antidiuretic effect. Precaution is needed in patients with coronary artery disease and/or hypertensive vascular disease, in patients with fluid and electrolyte disbalance, in patients with allergic rhinitis, nasal congestion, and upper respiratory infections who may experience decreased effectiveness (1). In the treatment of primary nocturnal enuresis or nocturia no fluid should be taken 1 hour before and 8 hours after desmopressin administration. Precaution is needed in pediatric patients. Testing of renal concentration capacity in children less than 1 year of age should be done only in hospital and with continuous surveillance. According to U.S. Food and Drug Administration desmopressin is classified in the pregnancy risk category B (3). In diuretic doses desmopressin does not have uterotonic effect. Physician should determine risk to benefit ratio for every individual case. Precaution is needed during lactation, considering that many of drugs are excreted in human milk (3).

CLINICAL STUDIES

Three children with primary nocturnal enuresis had resolution of this condition within 2 days after initiation of desmopressin in dose of 20 micrograms intranasally. One child had primary nocturnal enuresis only, while the other 2 had primary nocturnal enuresis and congenital nephrogenic diabetes insipidus. In patients with congenital nephrogenic diabetes insipidus, mutations in vasopressin-2 receptor (V₂R) or aquaporin-2 (AQP2) water-channel genes inactivate arginine-vasopressin proteins. Patients with this mutation are unable to concentrate their urine in response to secretion of arginine-vasopressin. Serum osmolality is therefore high and urinary osmolality low, despite high plasma arginine-vasopressin concentrations. After the 3 children were placed on desmopressin therapy, the child

with primary nocturnal enuresis slept through the night and did not wet the bed. The 2 youngsters with nephrogenic diabetes insipidus woke up during the night and went to the toilet to empty their bladder. All returned to their previous bed-wetting habits when desmopressin was temporarily halted. With restoration of desmopressin, all 3 ceased bed-wetting. Desmopressin may act outside of the renal area and may act in the central nervous system to resolve nocturnal enuresis (14). Results of a randomized, double-blind, placebo controlled cross-over study demonstrated that oral desmopressin given to elderly patients with nocturnal polyuria at bedtime (n=17) was associated with reduced nocturnal diuresis and nocturnal voiding and increased uninterrupted sleep. Patients with nocturnal urinary output $\geq 0,9$ ml/min and ≥ 2 nocturnal voids were eligible to participate in this study. Each patient had their dose titrated one week at a time beginning with 0,1 mg followed by 0,2 mg then 0,4 mg. Patients with nocturnal diuresis $\geq 0,5$ ml/min were allowed to progress to the next dose level. The optimal dose of oral desmopressin in this population was identified as 0,1 mg administered at bedtime with no dose-response relationship observed (15). Significant mean reductions in nocturnal diuresis and nocturnal voids were experienced by desmopressin patients compared to placebo after 2 weeks of therapy ($p < 0,001$). No change in 24-hour diuresis was observed. In patients with higher nocturnal contribution to the baseline 24-hour diuresis experienced greatest decreases in nocturnal diuresis with desmopressin therapy. The mean total number of hours slept per night was not changed by desmopressin treatment; however, the longest period of uninterrupted sleep was extended by 1,4 hours. No patient experienced serious adverse event during the study period. Likewise, the amount of sodium excretion, the temporal excretion pattern of sodium, and the difference in mean serum osmolality were not different between the placebo period and the desmopressin treatment period. No dose-response relationship was observed for desmopressin (16). Results of a randomized, double-blind, crossover, and placebo controlled study indicate that children with desmopressin resistant enuresis have nocturnal bladder instability yet some of these patients (5/33) respond to high-dose desmopressin therapy. Children 6 to 16 years of age, who had primary monosymptomatic enuresis at least 6 wet nights during baseline and less than 50% decrease in the number of wet nights while receiving desmopressin dose of 0,4 mg, were enrolled in the study. During the study, patients were treated with desmopressin 0,4 mg, desmopressin 0,8 mg, and placebo for 5

consecutive nights with a washout period of at least 48 hours between treatment periods. During double-blind therapy, the probability of enuresis and nocturia was highest with placebo compared to desmopressin 0,4 mg and desmopressin 0,8 mg ($p = 0,0001$). However, no difference between the two desmopressin groups was observed. The mean number of hours between bedtime and first bladder voiding during treatment periods was significantly smaller for placebo compared to desmopressin ($p < 0,0001$) but again no differences between the desmopressin groups were observed. Nine children were dry during all 5 nights of at least 1 of the 3 treatment periods and were treated with open-label high-dose desmopressin 0,8 mg. Complete dryness was achieved in 5 of these patients. Of 28 patients who received open-label desmopressin 0,4 mg at bedtime combined with oxybutynin 5 mg twice a day, 13 were complete responders and 7 were intermediate responders (number of wet nights decreased by more than 50% compared to baseline but still with enuretic accidents) (17). Intranasal desmopressin therapy administered at bedtime to a cohort of 7 children with extrophy-epispadias complex and nocturnal incontinence was associated with decreased urinary output at night and six of the seven achieved nocturnal dryness. All patients, aged 8 to 12 years, had daytime continence yet experienced bed wetting 7 nights per week. Desmopressin therapy was titrated from 10 to 30 μ g until patients were dry all night. Nighttime urinary output was decreased from a mean of 230 ml at baseline to 134 ml while on desmopressin. After 2 months of successful therapy, dose was down titrated to the minimum effective dose. Nocturnal dryness was achieved in 6 patients at 20 μ g desmopressin and 1 required 30 μ g. After initial 2 months, long-term therapy was successful at 5 to 10 μ g per night in 4 patients, 20 μ g in 2 patients and 30 μ g in 1 patient. At 14 months follow-up, all patients remained on desmopressin therapy. Six patients are dry at night while 1 still has nocturia. The only side effect reported was nosebleed in one patient. Body weight, arterial blood pressure, and serum electrolytes were not significantly modified on desmopressin therapy in this patients group (18). One trial (n=155, average age 8 years) employed intranasal desmopressin 20 μ g titrated to a maximum of 50 μ g if not dry within 48 hours, then continued for 4 to 6 weeks maintenance therapy. A gradual dosage reduction of 10 μ g per month was undertaken after 4 weeks of complete dryness. If relapse occurred during tapering or after cessation of therapy, previous dosage was resumed. After an average 28-week treatment duration and 18-month median follow-up, the response

rate of 85% included 71% who remained completely dry without relapse, 7% who achieved complete dryness with relapse, and 7% who showed some improvement (less than 3 enuretic episodes per week) (19). In a study of 25 patients (average age 14 years) with severe enuresis (5 nights/week at baseline), oral desmo-

pressin 200 to 400 µg applied for 6 months resulted in complete dryness in 8 of 23 evaluated patients (35%). An additional 30% and 17% achieved cure within 2 and 6 years after the study, respectively. After 7 years, in a follow-up, 9% still experienced enuresis and 9% required continuous desmopressin to maintain dryness (20).

CONCLUSION

Desmopressin is a drug of choice for substitution treatment of diabetes insipidus. Antidiuretic effect of desmopressin is a result of agonistic activity on V₂ receptors placed in tubules of the kidney. Molecular mechanism of action includes stimulation of adenilate cyclase and enhanced synthesis of cAMP. Except enhancing reabsorption of water in collecting tubules of kidney, desmopressin plays role in factor VIII release and it is plasmin activator. In addition, it is used in the treatment of coagulopathies, hemophilia A and von Willebrand's disease. Desmopressin is, mostly, well tolerated. The most common adverse effects are fluid retention, hyponatremia, seizures, abdominal cramps, headache, nausea, vomiting and epistaxis.

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