

COMPARISON OF DESMOPRESSIN (DDAVP) TABLET AND INTRANASAL SPRAY IN THE TREATMENT OF CENTRAL DIABETES INSIPIDUS

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ABSTRACT

Desmopressin is the drug of choice for treatment of central diabetes insipidus and most commonly it is used as intranasal spray. In this study, efficacy and side effects of oral desmopressin was compared with the intranasal spray. This study was before-after clinical trial on 14 outpatients (9 F, 5 M, age 14-50 Y) with central diabetes insipidus who had been treated with intranasal spray of desmopressin previously. Weight, pulse rate and blood pressure (sitting-standing), biochemical profile, serum electrolytes, 24h urine volume, specific gravity of urine and LFT was measured before and after 1 month study. Starting dose for each patient was one oral tablet of DDAVP (0.1 mg) per 8 hours. Paired Samples T-Test was used for data analysis. No clinically significant changes were found as regard to weight, pulse rate, blood pressure, blood chemistry, electrolyte and urinalysis. Single reported adverse effect was headache (43%) in tablet group and dyspnea (7%) in spray group. Both dosage forms were able to control diurnal polyuria and nocturnal polyuria. The antidiuretic dose-equivalence ratio for intranasal to oral desmopressin was 1:18. Spray was superior in terms of rapid onset of action and duration of antidiuretic action in 100% and 78% of cases (not significant), respectively. Tablets were more available and much more easily consumed as reported by patients, in 86% (P=0.0006). Treatment with tablets offers a good alternative to the intranasal route, especially in patients with chronic rhinitis or common cold and similar conditions.

Keywords: Central diabetes insipidus, Desmopressin, DDAVP.

INTRODUCTION

Diabetes insipidus (DI) is a rare metabolic disorder of water metabolism in which volume of fluid intake is not in balance with the urine output (1). There are two types of diabetes insipidus: central (also known as cranial or neurogenic diabetes insipidus) and nephrogenic. Central diabetes insipidus (CDI) results from deficient or low level of vasopressin (antidiuretic hormone) secretion (1, 2). This low level or lack of vasopressin is due to a malfunction or destruction in a part of brain, the posterior pituitary gland and hypothalamus, which release the hormone into blood-stream.

Etiologies of CDI include idiopathic causes (in about 50% of cases), familial, brain tumor (primary or secondary), head trauma, post neurosurgery in the area of pituitary or hypothalamus, infection such as encephalitis, vascular disorders like post partum necrosis, systemic disorders such as sarcoidosis, tumor metastases, and aneurysm (1,2). The condition can be acute and short in duration or chronic life-long problem.

Central diabetes insipidus is a polyuric syndrome that is identified by three features including

persistence of on inappropriately dilute urine in the presence of strong osmotic or nonosmotic stimulation for AVP secretion, absence of intrinsic renal disease, and a rise in urine osmolality after administration of vasopressin (2). CDI occurs a wide age range of people. Typical symptoms of CDI are presence of resistant excessive urination (polyuria; urine output greater than 3 ml/kg/day), which is followed by excessive thirst (polydipsia) (1, 3). The definitive diagnostic test is the water deprivation test, which can be used both to confirm the diagnosis and to distinguish between central and nephrogenic diabetes insipidus by response to a vasopressin analogue (1, 2). Following treatments are used to combat the CDI: balance fluid intake and urine output, replace antidiuretic hormone (vasopressin), and to find if possible, underlying brain disease (1).

For CDI, the treatment of choice is desmopressin (a synthetic vasopressin analogue), DDAVP or Minirin® (4, 5). It is available as parenteral, intranasal (drop or spray) and tablet forms (0.1, 0.2 mg) (1, 6-9).

Compared with pituitary vasopressin hormone, DDAVP not only has longer and much more potent antidiuretic action, but also has minimal side effects (3, 5). Because DDAVP tablet has

good absorption, good biologic effects and low side effects similar to that of intranasal spray, therefore treatment with tablets offers beneficial alternative to the intranasal route for CDI (4, 5, 10-19).

This study was performed to compare efficacy of oral tablet and intranasal spray of DDAVP in the treatment of CDI.

MATERIALS AND METHODS

This study was before-after clinical trial on 14 outpatients (9 F, 5 M, 14-50 Y) with established CDI who had been treated with intranasal spray of desmopressin previously. In this study, condition of diabetes insipidus in each patient was compared with himself in administration of intranasal mode with DDAVP tablet.

Inclusion criteria were: known established CDI and agreement for enrollment in the study. Water deprivation test was performed for definite diagnosis of CDI before beginning the study.

For differential diagnosis between CDI and Nephrogenic Diabetes Insipidus (NDI) in patients with excessive polyuria and excessive thirst, patients should be hospitalized for evaluation of body weight and base urine osmolality. Usually in this condition urine osmolality is less than 200 mOSL/kg/H₂O. After 6 hours of NPO, body weight and urine osmolality was reevaluated every one hour. During this period of the experiment intake of water was not allowed. When urine osmolality was reduced to less than 20% of base and was stable, or 5% dehydration, a subcutaneous injection of 1 µg of DDAVP (S.C) or a puff of intranasal DDAVP spray (each puff has 10 µg DDAVP) was administered.

After injection, if urine osmolality was raised to 2 times more than the base, the diagnosis of CDI was established. This test was performed for all 14 patients before beginning of the study.

Exclusion criteria were: CDI with following condition, cardiovascular disease, diabetes mellitus, seizures, kidney or liver disease, pregnancy.

At first, the patients were oriented about the aim and method of the study. After obtaining written informed consent a questionnaire including demographic characteristic, socioeconomic status, dosage of spray and number of nocturnal and daytime voids was completed for each participant. Each subject underwent a physical examination including measurement of body weight, pulse rate and blood pressure (sitting-standing). All examination was performed by a single physician. Biochemical profile, serum electrolytes, 24h urine volume, urine specific gravity and Liver Function Test (LFT) was measured for utilization of spray for each patient. Administration of spray in

previous dosage was continued in this stage. Immediately after sampling, utilization of spray was discontinued for one dosage. As soon as appearance of mild to moderate polyuria, one oral DDAVP tablet (0.1 mg) Q8h (half life=8-12 h) was prescribed. Washout time was limited to the minimum time that was required to prevent sever polyuria and hypotension.

In this stage, any adjustments to the dosage regimen were made either by telephone contact on the basis of general signs and symptoms, numbers of daytime and nocturnal voids, urine volume in 24h (by standard graduated gallon that was available for patient in home). When nocturnal polyuria and number of voids in daytime was controlled and 24h urine volume reached to the acceptable level (2-2.5 lit/day), DDAVP tablet dosage was recorded as topic maintenance dose. This maintenance dosage was continued in the reminder period of the study. After 4 weeks on tablets (at the end of the study), body weight, vital signs and the same laboratory tests (at the beginning of study while on intranasal treatment) were performed again. After the end of study, administration of tablet was discontinued, and administration of the spray was started with the same dose (before the study). Satisfaction was evaluated regarding to the problem in drug usage (storage, easy consumption, availability and side effects), change in nocturnal urination habits, decrease in urination frequency and volume.

Laboratory Methods: LFT was measured by Enzymatic Assay (Kimia Pajouhan.Co, Iran. kit), biochemical tests were performed by Calorimetric and serum electrolytes were determined by Flame Photometry.

The study protocol was approved by the medical ethics committee of the vice chancellor for research of Tehran University of Medical Sciences. Paired Samples T-Test was used for data analysis. P value was significant, if $p < 0.05$.

RESULTS

Fourteen patients (9 F, 5 M), 14-50y, mean 33 ± 13 y, participated in the study. No clinically significant changes were found in body weight, blood pressure or heart rate before, during or after the study. None of the patients had nocturnal polyuria. Dosage of spray was variable between 10-60 µg/day and in oral tablet was 15-750µg/day. Headache was the only side effect of oral DDAVP which was reported by 6 patients (43%). Headache was due to muscular spasm, usually unilateral and was localized in temporal region. Patients experienced a headache with the feeling of compression and tension and sometimes pulsatile headache, rarely accompanied with vomiting, nausea or teardrops. Headache began

Table 1: Median of results of 14 patients (C.D.I) in the beginning of the study (utilization of intranasal spray of DDAVP) and the end of study (utilization of DDAVP tablet) (mean± SD)

Tests	Mean results in DDAVP intranasal spray	Mean results in DDAVP tablet
Urine/V/24h (ml)	1958 ± 758	1720 ± 378
S.G. urine	1011 ± 6	1011 ± 4
SGOT (U/L)	26 ± 16	18 ± 7
SGPT (U/L)	24 ± 21	14 ± 15
ALKP (U/L)	221 ± 113	234 ± 176
Bi. Total (mg/dl)	0.6 ± 0.1	0.8 ± 0.4
Bi. Direct (mg/dl)	0.2	0.2
BUN (mg/dl)	12 ± 2	13 ± 4
Cr (mg/dl)	0.8 ± 0.2	0.8 ± 0.2
Na ⁺ serum (mg/dl)	142 ± 2	143 ± 3
K ⁺ serum (mg/dl)	4 ± 0.2	4.5 ± 0.2
Maintenance dose (µg/day)	30 ± 17	456 ± 189
Numbers of nocturnal voids	0.7 ± 1.4	0.9 ± 1.2

*Only significant statistical was in K⁺ serum (intranasal compared with tablet), P =0.006 by paired samples T-Test.

with the early dosage of tablet, but discontinued by using acetaminophen and continuation of DDAVP tablets. Also, in administration of intranasal dosage form, dyspnea was the only side effect which was reported by one patient (7%). She felt discomfort of breath and while inhaling spray. This side effect was discontinued by deep inhalation. During the one month study, no clinically significant changes were observed in laboratory tests including LFT, biochemical tests, serum electrolytes and urine analysis. DDAVP tablet similar to intranasal spray of DDAVP had the ability to control urine volume and correct urine specific gravity to normal level (Table1).

The only significant statistic difference during this period in comparison with utilization of intranasal spray was changes in serum potassium (p=0.006). Tablet was more available and much more easily consumed according to patients, (86%, p=0.00067). However spray was reported superior in terms of rapid onset of action and duration of antidiuretic action in 100% and 78% of cases (p=0.054), respectively. The antidiuretic dose-equivalence ratio for intranasal to oral desmopressin was calculated in each patient and then mean ratio was determined by descriptive test in all patients. Finally, the antidiuretic dose-equivalence ratio for intranasal to oral (0.1 mg) of desmopressin was 1:18.

DISCUSSION

According to the results, onset, ability and duration of antidiuretic action by the spray of DDAVP is much more than its tablet, but tablet similar to spray has the ability to control and correct polyuria, nocturnal polyuria and urine specific gravity in CDI patients.

Although the bioavailability of oral desmopressin is low and is about 1-5% (due to absorption of small proportion through the gut in comparison with nasal mucosa), but it is sufficient to induce an antidiuresis (urine osmolality greater than 400 mOsm/kg), lasting 7-9 hours in healthy subjects and in patients with diabetes insipidus (10).

During a dose ranging study in hospital, followed by 6 months of treatment at home (17), each oral DDAVP tablet proved to be as effective as the intranasal spray which was preferred by the patients. Even doses as small as 12.5 µg, had an effect on diuresis and urine osmolality.

The safety and efficacy of long-term treatment with oral desmopressin in 8 patients with CDI has been reported previously (13). The efficacy of the desmopressin tablet was very similar to intranasal mode after 1 and 3.5 years of treatment. These results were repeated in another study with 7-years follow-up of patients with nocturnal enuresis (20). In the first study, the disease was well controlled in all cases and mean daily urine volume reached to 1.7 Lit, with absence of nocturnal polyuria. There was no relationship between the oral dose required and the previous intranasal dose, or the age or weight of the patient. No adverse reactions or clinically important changes in laboratory values were reported (13). According to results it was found that long-term oral desmopressin therapy is safe and seems to have better response in long term treatment. Oral desmopressin had a clinically significant effect on the cure rate, which maintained after cessation of therapy.

From a 1-year prospective study in 10 Chinese adults with CDI which had been controlled previously by intranasal desmopressin, oral desmopressin produced and maintained a stable, satisfactory comparable antidiuresis there by (21).

The oral treatment was well tolerated, with no events warranting drug withdrawal. In one study, in which the efficacy of 0.1 and 0.4 mg oral desmopressin during 3 weeks were compared with placebo (22), the following results were obtained:

- A reduction of at least 50% in the mean numbers of nocturnal voids in 39% of patients with desmopressin compared to 5% in patients with placebo ($p < 0.0001$).
- Decrease in the mean numbers of voids per night by 44% with desmopressin compared to 15% with placebo ($p < 0.0001$).

The use of oral desmopressin was investigated in 12 patients with diabetes insipidus (23) who were previously well controlled with intranasal therapy. The oral dose of desmopressin was increased until the daily urinary output volumes became equal to those which was produced during intranasal therapy. The antidiuretic dose-equivalence ratio for intranasal: oral desmopressin ranged between 1:15 and 1:30 (mean ratio 1:18). This ratio is in agreement with previous studies (21, 24-26). In enuretic children (1:20) and in 10 Chinese adults, the bioequivalent intranasal /oral ratio was 1:16.

In our study, maximum doses of oral desmopressin (0.1 mg) tablet and intranasal were 800 μ g/day and 60 μ g/day, respectively. We found a significant relation between previous intranasal and present oral daily dosages, ratio 1:18. Also the required dose of oral route administration varied from patient to patient, on the basis of vital signs, urine volume in 24 h and its specific gravity, and the dosage of DDAVP tablets had to be determined for each individual patient and adjusted according to the diurnal pattern of response (10).

Some patients with diabetes insipidus like school-aged children are sometimes unable to use spray because of, higher prevalence of upper respiratory tract infections or colds per year, seasonal allergies or similar conditions that result in nasal congestion which impairs absorption of the nasal spray. In addition practical problems for storage of nasal spray which must be kept in a refrigerator these make the oral formulation to offer a beneficial alternative to the intranasal route (5, 14, 16, 20, 26). However the problem with oral route of administration is extremely low bioavail-

ability (1- 5%) compared to intranasal DDAVP. Therefore much higher doses of the oral form (10-20 times) than the established intranasal dose is required to produce the same antidiuretic effects which have been achieved by intranasal desmopressin (10).

Efficacy and tolerability of oral desmopressin were evaluated in 12 adult patients suffering from CDI (19). No significant changes in body weight, arterial blood pressure and blood chemistry parameters were detected over the whole period of administration and only some slight side-effects occurred (19,26). These findings were in agreement to our study.

Total adverse events associated with desmopressin treatment are usually mild and infrequent (19) and high doses of desmopressin have produced transient headache and nausea. These symptoms disappear by reduction in dosage (10). Common adverse effects ($> 1/100$) by oral dosage are headache (22). These results were confirmed by the present study. The only side effect of the spray dosage form was dyspnea.

One clinical trial study (10) reported elevation of serum AST levels in 4/16 patients 6 months after commencing oral desmopressin therapy (200-600 μ g/day). Two of these patients had exhibited baseline levels of AST that were above the normal range and all 4 patients had normal AST levels on repeat test at 9th months, even though desmopressin administration was continued. The possibility of desmopressin adverse effect on serum enzymes is therefore remote.

In addition, consumption of DDAVP tablets was much more easily (orally) and titration of dosage by users compared with intranasal spray mode was more accurate. DDAVP tablets don't require to be kept in refrigerator (against spray). Similar to spray, oral mode is safe with low side effects which can be controlled. Treatment with DDAVP tablet offers not only acceptable drug for use but it is also a good alternative to the intranasal route in CDI, especially in patients with acute or chronic rhinitis or traveling to tropical areas.

However, due to short duration of study and the absence patients with severe central diabetes insipidus in our study, these results can not be generalized.

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